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(\$7) Abstract

The present invention relates to subtilisin (309) variants having a modified amino acid sequence of wild-type subtilisin (309) amino acid sequence, the wild-type amino acid sequence comprising a first loop region, a second loop region, a third loop region, a fourth loop region, a fifth loop region and a sixth toop region, wherein the modified amino acid sequence comprises different amino acids than that occurring in wild-type subtilisin (309) (i.e., substitution) at specifically identified positions in one or more of the loop regions whereby the subtilisin (309) variant has decreased adsorption to, and increased hydrolysis of, an insoluble substrate as compared to the wild type subtilisin (309). The present invention also relates to DNA sequence encoding such subtilisin (309) variants. The present invention also relates to compositions comprising such subtilisin (309) variants for cleaning a variety of surfaces.

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SUBTILISIN 309 VARIANTS HAVING DECREASED ADSORPTION AND INCREASED HYDROLYSIS

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TECHNICAL FIELD

The present invention relates to novel enzyme variants useful in a variety of cleaning compositions, and the genes encoding such enzyme variants.

BACKGROUND

Enzymes make up the largest class of naturally occurring proteins. Each class of enzyme generally catalyzes (accelerates a reaction without being consumed) a different kind of chemical reaction. One class of enzymes known as proteases, are known for their ability to hydrolyze (break down a compound into two or more simpler compounds with the uptake of the H and OH parts of a water molecule on either side of the chemical bond cleaved) other proteins. This ability to hydrolyze proteins has been taken advantage of by incorporating naturally occurring and protein engineered proteases as an additive to laundry detergent preparations. Many stains on clothes are proteinaceous and wide-specificity proteases can substantially improve removal of such stains.

Unfortunately, the efficacy level of these proteins in their natural, bacterial environment, frequently does not translate into the relatively unnatural wash environment. Specifically, protease characteristics such as thermal stability, pH stability, oxidative stability and substrate specificity are not necessarily optimized for utilization outside the natural environment of the enzyme.

The amino acid sequence of the protease determines the characteristics of the protease. A change of the amino acid sequence of the protease may alter the properties of the enzyme to varying degrees, or may even inactivate the enzyme, depending upon the location, nature and/or magnitude of the change in the amino acid sequence. Several approaches have been taken to alter the wild-type amino acid sequence of proteases in an attempt to improve their properties, with the goal of increasing the efficacy of the protease in the wash environment. These approaches include altering the amino acid sequence to enhance thermal stability and to improve oxidation stability under quite diverse conditions.

Despite the variety of approaches described in the art, there is a continuing need for new effective variants of proteases useful for cleaning a variety of surfaces.

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2 Objects of the Present Invention

It is an object of the present invention to provide subtilisin 309 enzyme variants having improved hydrolysis versus the wild-type of the enzyme.

It is also an object of the present invention to provide cleaning compositions comprising these subtilisin 309 enzyme variants.

SUMMARY

The present invention relates to subtilisin 309 variants having a modified amino acid sequence of wild-type subtilisin 309 amino acid sequence, the wild-type amino acid sequence comprising a first loop region, a second loop region, a third loop region, a fourth loop region, a fifth loop region and a sixth loop region; wherein the modified amino acid sequence comprises different amino acids than that occurring in wild-type subtilisin 309 (i.e., substitution) at specifically identified positions in one or more of the loop regions whereby the subtilisin 309 variant has decreased adsorption to, and increased hydrolysis of, an insoluble substrate as compared to the wild-type subtilisin 309. The present invention also relates to DNA sequences encoding such subtilisin 309 variants. The present invention also relates to compositions comprising such subtilisin 309 variants for cleaning a variety of surfaces

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A and Figure 1B depict the amino acid sequences of subtilisin BPN' and subtilisin 309. The top line represents the amino acid sequence of subtilisin BPN' (SEQ ID NO:2), which is derived from Bacillus amytoliquefaciens; the bottom line represents the amino acid sequence of subtilisin 309 (SEQ ID NO:1), which is derived from Bacillus lentus. The symbol * in the sequence for subtilisin 309 denotes the absence of specific amino acid residues as compared to subtilisin BPN'.

DESCRIPTION

Subtilisin 309 Variants

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This invention pertains to subtilisin enzymes, in particular subtilisin 309. that have been modified by mutating the various nucleotide sequences that code for the enzyme, thereby modifying the amino acid sequence of the The modified subtilisin enzymes (hereinafter, "subtilisin 309 variants") of the present invention have decreased adsorption to and increased hydrolysis of an insoluble substrate as compared to the wild-type subtilisin. The present invention also pertains to the mutant genes encoding for such subtilisin 309 variants

When refering to the amino acid sequence of native subtilisin 309

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(having 269 amino acid residues), the amino acid sequence of subtilisin BPN' (having 275 amino acid residues) is frequently used as the standard. The use of "BPN" numbering" has become the coventional method for identifying residue positions in all subtilisins. The amino acid sequences for native 5 subtilisin BPN and native subtilisin 309 are set forth in Figs 1A and 1B. The symbol "" in the sequence for subtilisin 309 in Figs 1A and 1B denotes the absence of specific amino acid residues compared to native subtilisin BPN'. However, for purposes of discussion herein, reference to amino acid positions shall be based on "true" subtilisin 309 numbering (e.g., refer to SEQ ID NO:1, discussed below).

The subtilisin 309 enzymes of this invention belong to a class of enzymes known as proteases. A protease is a catalyst for the cleavage of peptide bonds. One type of protease is a serine protease. A serine protease is distinguished by the fact that there is an essential serine residue at the active site

The observation that an enzyme's rate of hydrolysis of soluble substrates increases with enzyme concentration is well documented. It would therefore seem plausible that for surface bound substrates, such as is encountered in many cleaning applications, the rate of hydrolysis would increase with increasing surface concentration. This has been shown to be the case. (Brode, P.F. III and D. S. Rauch, LANGMUR, "Subtilisin BPN": Activity on an Immobilized Substrate", Vol. 8, pp. 1325-1329 (1992)). In fact, a linear dependence of rate upon surface concentration was found for insoluble substrates when the surface concentration of the enzyme was varied. (Rubingh, D. N. and M. D. Bauer, "Catalysis of Hydrolysis by Protesses at the Protein-Solution Interface," in POLYMER SOLUTIONS, BLENDS AND INTERFACES, Ed. by I, Noda and D. N. Rubingh, Elsevier, p. 464 (1992)). Surprisingly, when seeking to apply this principle in the search for variant proteases which give better cleaning performance, we did not find that enzymes which adsorb more give better performance. In fact, we surprisingly determined the opposite to be the case: decreased adsorption by an enzyme to a substrate resulted in increased hydrolysis of the substrate (i.e., better cleaning performance).

While not wishing to be bound by theory, it is believed that improved performance, when comparing one variant to another, is a result of the fact that enzymes which adsorb less are also less tightly bound and therefore more highly mobile on the surface from which the insoluble protein substrate is to be removed. At comparable enzyme solution concentrations, this increased mobility is sufficient to outweigh any advantage that is conferred by delivering WO 95/30011 PCT/US95/94769

a higher concentration of enzyme to the surface.

The mutations described herein are designed to change (i.e., decrease) the adsorption of the enzyme to surface-bound soils. In subtilisin 309, certain amino acids form exterior loops on the enzyme molecule. For purposes of discussion, these loops shall be referred to as the first, second, third, fourth and fifth loop regions. Specifically, positions 57-64 form the first loop region; positions 93-105 form the second loop region; positions 124-131 form the third loop region; positions 152-161 form the fourth loop region; positions 181-185 form the fifth loop region; and positions 193-214 form the sixth loop region (position numbering analagous to positions in the amino acid sequence for wild-type subtilisin 309 (SEQ ID NO:1))

It believed that these loop regions play a significant role in the adsorption of the enzyme molecule to a surface-bound peptide, and specific mutations in one or more of these loop regions will have a significant effect or this adsorption. While not wishing to be bound by theory, it is believed that the loop regions are important to the adsorption of the subtilisin 309 molecule for at least two reasons. First, the amino acids which comprise the loop regions can make close contacts with any surfaces to which the molecule is exposed. Second, the proximity of the loop regions to the active-site and binding packet of the subtilisin 309 molecule gives them a role in the catalytically productive adsorption of the enzyme to surface-bound substrates (peptides/protein soils).

The following is a list of abbreviations used herein to describe amino acids:

	Amino Acid T	hree-letter Abbreviation	One-letter Symbol
	Alanine	Ala	Α
	Arginine	Arg	R
	Asparagine	Asn	N
5	Aspartic Acid	Asp	D
	Asparagine or Aspartic	Acid Asp	D
	Cysteine	Cys	C
	Glutamine	Gln	Q
	Glutamic Acid	Glu	Ε
10	Giutamine or Glutamic /	Acid Glx	Z
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	lle	}
	Leucine	Leu	L
15	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Phe	F
	Serine	Ser	S
20	Threonine	Thr	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	٧
	No amino acid at position	n Xaa	*

As used herein, "variant" means an enzyme having an amino acid sequence which differs from that of wild-type.

As used herein, "mutant subtilisin 309 DNA sequence" means a DNA sequence coding for a subtilisin 309 variant.

As used herein, "wild-type subtilisin 309" refers to an enzyme represented by SEQ ID NO:1. The amino acid sequence for subtilitish 309 is further described in World Patent Publication 89/06279 (1989), incorporated herein by reference. See also, World Patent Publication 94/02618, published February 3, 1994 by Mulleners et al.

As used herein, the term "subtilisin 309 wild-type amino acid sequence" encompasses SEQ ID NO:1 as well as SEQ ID NO:1 having modifications to the amino acid sequence other than at any of positions 57-64, 93-105, 124-131, 152-161, 181-185 and 193-214.

As used herein, "more hydrophilic amino acid" refers to any other amino

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acid having greater hydrophilicity than a subject amino acid with reference to the hydrophilicity table below. The following hydrophilicity table (Table 1) lists amino acids in descending order of increasing hydrophilicity (see Hopp, T.P., and Woods, K.R., "Prediction of Protein Antigenic Determinants from Amino s Acid Sequences", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCE USA, Vol. 78, pp. 3624-3628, 1981, incorporated herein by reference).

TABLE 1

	Amino Acid	Hydrophilicity Value	
	Trp	-3,4	
10	Phe	-2.5	
	Tyr	-2.3	
	Leu, Ile	-1.8	
	Val	-1.5	
	Met	-1.3	
15	Cys	-1.0	
	Ala, His	-0.5	
	Thr	-0.4	
	Pro, Gly	-0.0	
	Gln, Asn	0.2	
20	Ser	0.3	
******	Arg*, Lys*, Glu*, Asp*	3.0	

Table 1 also indicates which amino acids carry a charge (this characteristic being based on a pH of from about 8-9). The positively charged amino acids are Arg and Lys, the negatively charged amino acids are Glu and Asp, and the remaining amino acids are neutral. In a preferred embodiment of the present invention, the substituting amino acid is either neutral or negatively charged, more preferably negatively charged (i.e., Glu or Asp).

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Therefore, for example, the statement "substitute Gln with an equally or more hydrophilic amino acid which is neutral or has a negative charge" means Gln would be substituted with Asn (which is equally hydrophilic to Gln), or Ser, Glu or Asp (which are more hydrophilic than Gln); each of which are neutral or have a negative charge, and have a greater hydrophilicity value as compared to Gln. Likewise, the statement "substitute Pro with a more hydrophilic amino acid which is neutral or has a negative charge" means Pro would be substituted with Gln. Asn. Ser. Glu or Asp.

A. Loop Region 6 Substitution Variants

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1. Variants comprising at least one amino acid substitution

In one embodiment of the present invention, the subtilisin 309 variant has a modified amino acid sequence of subtilisin 309 wild-type amino acid sequence, wherein the modified amino acid sequence comprises a substitution at one or more of positions 193, 194, 195, 196, 197, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 or 214; whereby the subtilisin 309 variant has decreased adsorption to, and increased hydrolysis of, an insoluble substrate as compared to the wild-type subtilisin 309. Preferably, the positions having a substituted amino acid are 193, 194, 195, 196, 199, 201, 202, 203, 204, 205, 206 or 209; more preferably, 194, 195, 196, 199 or 201.

Preferably, the substituting amino acid for position 193 is Ala, Asn, Asp, Cvs. Gln. Glu. Glv. His. Pro. Ser or Thr.

Preferably, the substituting amino acid for position 194 is Asn, Asp, Gln, Is Glu, Glv, His. Pro. Ser or Thr.

Preferably, the substituting amino acid for position 195 is Asn, Asp, Gln, Glu, Gly, Ser.

Preferably, the substituting amino acid for position 196 is Asn, Asp, Gln, Glu, Pro or Ser.

20 Preferably, the substituting amino acid for position 197 is Ala, Asp, Cys, Gln. Glu. Glv. His. Met. Pro or Ser.

Preferably, the substituting amino acid for position 199 is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 200 Asn, Asp, Glu or

25 Ser. Preferably, the substituting amino acid for position 201 is Asp or Glu. Preferably, the substituting amino acid for position 202 is Asn, Asp, Gln,

Glu, Gly, Pro or Ser.

Preferably, the substituting amino acid for position 203 is Ala, Asn, Asp,
Gln, His, Ile, Met, Pro or Ser.

Preferably, the substituting amino acid for position 204 is Asn, Asp, Gln, Glu, Gly or Ser.

Preferably, the substituting amino acid for position 205 is Asn, Asp, Gln, Glu, Pro or Ser.

95 Preferably, the substituting amino acid for position 206 is Asp or Glu. Preferably, the substituting amino acid for position 207 is Asn, Asp, Gln, Glu, Gly, Pro or Ser. WO 95/30011 PCT/US95/04760

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Preferably, the substituting amino acid for position 208 is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Pro or Val.

Preferably, the substituting amino acid for position 209 is Asn, Asp, gln, Glu, gly, His, Pro, Ser or Thr.

5 Preferably, the substituting amino acid for position 210 is Asp or Glu. Preferably, the substituting amino acid for position 211 is Ala, Asn, Asp, Cys, Gln, Gly, His, Ile, Met, Pro, Ser, Thr or Val.

Preferably, the substituting amino acid for position 212 is Glu.

Preferably, the substituting amino acid for position 213 is Asn, Asp, Gln, 10 Glu, Pro or Ser.

Preferably, the substituting amino acid for position 214 is Asn, Asp, Gln, Glu, Gly, Pro or Ser.

More preferably, the substituting amino acid for any of positions 193, 194, 195, 196, 197, 199, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 and 214 is, with reference to Table 1, is neutral or negatively charged and equally or more hydrophilic, preferably more hydrophilic, than the amino acid at the subject position in wild-type subtilisin 309.

More preferably still, the substituting amino acid for any of positions 193, 194, 195, 196, 197, 199, 200, 201, 202, 204, 205, 206, 207, 208, 209, 210, 212, 213 and 214 is Asp or Glu; and the substituting amino acid for positions 203 and 211 is Asp.

Variants comprising at least two amino acid substitutions

In another embodiment of the present invention, the subtilisin 309 variant has a modified amino acid sequence of subtilisin 309 wild-type amino acid sequence, wherein the modified amino acid sequence comprises a substitution at two or more of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 or 214; whereby the subtilisin 309 variant has decreased adsorption to, and increased hydrolysis of, an insoluble substrate as compared to wild-type subtilisin 309. Preferably, the positions having a substituting amino acid are 193, 194, 195, 199, 201, 202, 203, 204, 205, 206, or 209; more preferably, positions 194, 195, 196, 211 or 213.

Preferably, the substituting amino acid for position 193 is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Met, Pro, Ser and Thr.

Preferably, the substituting amino acid for position 194 is Asn, Asp, Gln, Glu, Gly, His, Pro, Ser or Thr.

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Preferably, the substituting amino acid for position 195 is Asn, Asp, Gln, Glu, Gly or Ser.

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Preferably, the substituting amino acid for position 196 is Asn. Asp. Gln. Glu. Pro or Ser.

Preferably, the substituting amino acid for position 197 is Ala, Asn, Asp, Cvs. Gln. Glu. Glv. His. Met. Pro. Ser or Thr.

S Preferably, the substituting amino acid for position 198 is Asp. Gln. Glu. or Ser.

Preferably, the substituting amino acid for position 199 is Ala. Asn. Asp. Cvs. Gln. Glu. Glv. His. Met. Pro. Ser or Thr.

Preferably, the substituting amino acid for position 200 is Asn, Asp, Glu 10 or Ser.

Preferably, the substituting amino acid for position 201 is Asp or Glu.

Preferably, the substituting amino acid for position 202 is Asn. Asp. Gln. Glu, Gly, Pro or Ser.

Preferably, the substituting amino acid for position 203 is Ala, Asn, Asp, 15 Cys. Gln. Glu. Glv. His, Ile. Met. Pro. Ser or Thr.

Preferably, the substituting amino acid for position 204 is Asn, Asp, Gln, Glu, Gly or Ser.

Preferably, the substituting amino acid for position 205 is Asn, Asp, Gin, Glu. Pro or Ser.

Preferably, the substituting amino acid for position 206 is Asp or Glu.

Preferably, the substituting amino acid for position 207 is Asn. Asp. Gln. Glu, Gly, Pro or Ser.

Preferably, the substituting amino acid for position 208 is Ala. Asn. Asp. Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Pro or Val.

Preferably, the substituting amino acid for position 209 is Asn. Asp. Gln. Glu, Glv, His, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 210 is Asp or Glu. Preferably, the substituting amino acid for position 211 is Ala. Asn. Asp. Cys, Gin, Glu, Gly, His, IIe, Met, Pro, Ser, Thr or Val.

Preferably, the substituting amino acid for position 212 is Asp. Gin. Glu or Ser. However, if position 211 is substituted with Asn, Glu or Val. then position 212 is not substituted with Asp:

Preferably, the substituting amino acid for position 213 is Asn, Asp, Gin, Glu. Pro or Ser.

Preferably, the substituting aming acid for position 214 is Asn. Asp. Gln. Glu. Glv. Pro or Ser.

More preferably, the substituting amino acid for any of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208,

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209, 210, 211, 212, 213 or 214 is, with reference to Table 1, is neutral or negatively charged and equally or more more hydrophilic, preferably more hydrophilic, than the amino acid at the subject position in wild-type subtilisin 309.

More preferably still, the substituting amino acid for any of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 or 214 is Asp and Glu.

3. Variants comprising at least three amino acid substitutions

In another embodiment of the present invention, the subtilisin 309 variant has a modified amino acid sequence of subtilisin 309 wild-type amino acid sequence, wherein the modified amino acid sequence comprises a substitution at three or more of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 or 214; whereby the subtilisin 309 variant has decreased adsorption to, and increased hydrolysis of, an insoluble substrate as compared to wild-type subtilisin 309. Preferably, the positions having a substituting amino acid are 193, 194, 195, 199, 201, 202, 203, 204, 205, 206, or 209; more preferably, positions 194, 195, 196, 211 or 213.

Preferably, the substituting amino acid for position 193 is Ala, Asn, Asp, Cvs, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 194 is Asn, Asp, Gln, Glu, Gly, His, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 195 is Asn, Asp, Gln, Glu, Gly or Ser.

25 Preferably, the substituting amino acid for position 196 is Asn, Asp, Gln, Glu. Pro or Ser.

Preferably, the substituting amino acid for position 197 is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 198 is Asp, Gln, Glu or Ser.

Preferably, the substituting amino acid for position 199 is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 200 Asn, Asp, Glu or Ser,

35 Preferably, the substituting amino acid for position 201 is Asp or Glu. Preferably, the substituting amino acid for position 202 is Asn, Asp, Gln, Glu, Gly, Pro or Ser.

Preferably, the substituting amino acid for position 203 is Ala, Asn, Asp,

Cvs. Gln. Glu. Glv. His. Ite. Leu. Met. Pro. Ser. Thr or Val.

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Preferably, the substituting amino acid for position 204 is Asn, Asp, Gln. Glu, Gly or Ser.

Preferably, the substituting amino acid for position 205 is Asn. Asp. Gln. Glu. Pro or Ser.

Preferably, the substituting amino acid for position 206 is Asp or Glu. Preferably, the substituting amino acid for position 207 is Asn. Asp. Gin. Glu, Glv, Pro or Ser.

Preferably, the substituting amino acid for position 208 is Ala, Asn, Asp, Cys, Gin, Giu, Gly, His, Ile, Leu, Met, Pro. Thr or Val.

Preferably, the substituting amino acid for position 209 is Asn. Asp. Gln. Glu, Glv, His, Pro, Ser or Thr.

Preferably, the substituting amino acid for position 210 is Asp or Glu.

Preferably, the substituting amino acid for position 211 is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Met, Pro, Ser, Thr or Val. 15

Preferably, the substituting amino acid for position 212 is Asp. Gln. Glu or Ser.

Preferably, the substituting amino acid for position 213 is Asn, Asp. Gln. Glu, Pro or Ser.

Preferably, the substituting amino acid for position 214 is Asn, Asp, Gln, Glu, Gly, Pro or Ser.

More preferably, the substituting amino acid for any of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 or 214 is, with reference to Table 1, is neutral or negatively charged and equally or more hydrophilic, preferably more hydrophilic, than the amino acid at the subject position in wild-type subtilisin 309.

More preferably still, the substituting amino acid for any of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 208, 209, 210, 211, 212, 213 or 214 is Asp or Glu.

Multi-Loop Regions Substitution Variants

In another embodiment of the present invention, the subtilisin 309 variant has a modified amino acid sequence of subtilisin 309 wild-type amino acid sequence, wherein the modified amino acid sequence comprises a substitution at one or more positions in one or more of the first, second, third, fourth, or fifth loop regions; whereby the subtilisin 309 variant has decreased adsorption to, and increased hydrolysis of, an insoluble substrate as compared to the wild-type subtilisin 309.

In another embodiment of the present invention, the subtilisin 309 variant further comprises one or more substitutions to the sixth loop region.

In a preferred embodiment of the present invention, the substituting amino acid for one or more of the positions in one or more of the loop regions is, with reference to Table 1, neutral or negatively charged and equally or more hydrophilic, preferably more hydrophilic, than the amino acid at the subject position in the wild-type amino acid sequence.

1. Substitutions in the First Loop Region

When a substitution occurs in the first loop region, the substitution occurs at one or more of positions 57, 58, 59, 60, 61, 63, or 64.

When a substitution occurs at position 57, the substituting amino acid is Asn, Asp, Glu or Ser.

When a substitution occurs at position 58, the substituting amino acid is Glu

15 When a substitution occurs at position 59, the substituting amino acid is Asn, Asp, Glu, Pro or Ser.

When a substitution occurs at position 60, the substituting amino acid is Asp. Gin, Giu or Ser.

When a substitution occurs at position 61, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

When a substitution occurs at position 63, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

When a substitution occurs at position 64, the substituting amino acid is Asn, Asp, Glu, Glu, Gly, Pro or Ser.

25 2. Substitutions in the Second Loop Region

When a substitution occurs in the second loop region, the substitution occurs at one or more of positions 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, or 105.

When a substitution occurs at position 93, the substituting amino acid is 38. Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

When a substitution occurs at position 94, the substituting amino acid is Ala, Asn, Asp, Cys, Gin, Glu, Gly, His, Ile, Met, Pro, Ser, Thr or Val.

When a substitution occurs at position 95, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

35 When a substitution occurs at position 96, the substituting amino acid is Asn, Asp, Gln, Glu, Gly, His, Pro, Ser or Thr.

When a substitution occurs at position 97, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 98, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

When a substitution occurs at position 99, the substituting amino acid is Asp or Glu

When a substitution occurs at position 100, the substituting amino acid is Asn. Asp. Glu. Pro or Ser.

When a substitution occurs at position 101, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 102, the substituting amino acid is Ala, Asn, Asp, Cvs, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

When a substitution occurs at position 103, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 104, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 105, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Leu, Met, Pro, Ser, Thr or Val.

3. Substitutions in the Third Loop Region

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When a substitution occurs in the third loop region, the substitution occurs at one or more of positions 124, 125, 126, 127, 128, 129, 130 or 131.

20 When a substitution occurs at position 124, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Met, Pro, Ser, Thr or Val.

When a substitution occurs at position 125, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

When a substitution occurs at position 126, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 127, the substituting amino acid is Asn, Asp, Gln, Glu, Gly or Ser.

When a substitution occurs at position 128, the substituting amino acid is Aso or Glu.

When a substitution occurs at position 129, the substituting amino acid is Asn. Asp. Gin. Glu. Giv or Ser.

When a substitution occurs at position 130, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 131, the substituting amino acid is Asn, Asp, Gln, Glu, Gly, His, Pro, Ser, Thr.

Substitutions in the Fourth Loop Region

When a substitution occurs in the fourth loop region, the substitution occurs at one or more of positions 152, 153, 154, 155, 156, 157, 158, 159, 160

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or 161.

When a substitution occurs at position 152, the substituting amino acid is Asn. Asp. Gln. Glu. Pro or Ser.

When a substitution occurs at position 153, the substituting amino acid is Asp. Gln. Glu or Ser.

When a substitution occurs at position 154, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 155, the substituting amino acid is Asn. Asp. Gin. Glu. Pro or Ser.

When a substitution occurs at position 156, the substituting amino acid is Asn. Asn. Gln. Glv. His. Pro. Ser or Thr.

When a substitution occurs at position 157, the substituting amino acid is Asn, Asp, Gin, Glu, Pro or Ser.

When a substitution occurs at position 158, the substituting amino acid is Asp or Giu.

When a substitution occurs at position 159, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Leu, Met, Pro, Ser, Thr or Val.

When a substitution occurs at position 160, the substituting amino acid is Asp or Giu.

20 When a substitution occurs at position 161, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Pro, Ser, Thr or Val.

5. Substitutions in the Fifth Loop Region

When a substitution occurs in the fifth loop region, the substitution occurs at one or more of positions 181, 182, 183, 184 or 185.

25 When a substitution occurs at position 181, the substituting amino acid is Asn, Asp, Gln, Glu, Gly, His, Pro, Ser or Thr.

When a substitution occurs at position 182, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 183, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Pro, Ser, Thr, Tyr or Val.

When a substitution occurs at position 184, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 185, the substituting amino acid is Asn. Asp. Glu or Ser.

Substitutions in the Sixth Loop Region

When a substitution occurs in the sixth loop region, in conjunction with one or more substitutions in one or more of the preceding five loop regions,

the substitution occurs at one or more of positions 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 or 214.

When a substitution occurs at position 193, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Gly, His, Met, Pro, Ser or Thr.

When a substitution occurs at position 194, the substituting amino acid is Asn, Asp, Gln, Giu, Gly, His, Pro, Ser or Thr.

When a substitution occurs at position 195, the substituting amino acid is Asn, Asp, Gln, Glu, Gly or Ser.

When a substitution occurs at position 196, the substituting amino acid is Asn, Asn, Gln, Glu, Pro or Ser.

When a substitution occurs at position 197, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Met, Pro, Ser or Thr.

When a substitution occurs at position 198, the substituting amino acid is Asp, Gln, Glu or Ser.

When a substitution occurs at position 199, the substituting amino acid is Ala, Asn, Asp, Cvs. Gln. Glu. Glv. His. Met. Pro. Ser or Thr.

When a substitution occurs at position 200, the substituting amino acid is Asn, Asp, Glu or Ser.

When a substitution occurs at position 201, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 202, the substituting amino acid is Asn, Asp, Gin, Glu, Gly, Pro or Ser.

When a substitution occurs at position 203, the substituting amino acid is Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Pro, Ser, Thr or Val.

When a substitution occurs at position 204, the substituting amino acid is Asn, Asp, Gin, Giu, Giy or Ser.

When a substitution occurs at position 205, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

30 When a substitution occurs at position 206, the substituting amino acid is Asp or Glu.

When a substitution occurs at position 207, the substituting amino acid is Asn, Asp, Gln, Glu, Gly, Pro or Ser.

When a substitution occurs at position 208, the substituting amino acid is Ala. Asn. Asp. Cvs. Gln. Glv. Glv. His. Ile. Leu. Met. Pro. Ser. Thr or Val.

When a substitution occurs at position 209, the substituting amino acid is Asn, Asp, Gln, Glu, Glly, His, Pro, Ser or Thr.

When a substitution occurs at position 210, the substituting amino acid

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is Asp or Giu.

When a substitution occurs at position 211, the substituting amino acid is Ala. Asn. Asp. Cvs. Gin. Glu. Gly. His. Ile. Met. Pro. Ser. Thr or Val.

When a substitution occurs at position 212, the substituting amino acid is Asp, Gln, Glu or Ser,

When a substitution occurs at position 213, the substituting amino acid is Asn, Asp, Gln, Glu, Pro or Ser.

When a substitution occurs at position 214, the substituting amino acid is Asn, Asp, Gln, Glu, Gly, Pro or Ser

10 C. Additional substitutions at positions other than the loop regions

As indicated hereinbefore, in addition to the one or more substitutions made to the first, second, third, fourth, fifth and/or sixth loop regions of wild-type subtilisin 309, substitutions may be made at positions other than position in such loop regions (hereafter referred to as "additional substitution"). In another embodiment of the present invention, the subtilisin 309 variant has a modified amino acid sequence of subtilisin 309 wild-type amino acid sequence wherein, in addition to being substituted at one or more positions in one or more of the above-discussed foop regions, there is substitution at position 74. The additional substitution may occur at position 74 alone (preferred), or in combination with one or more additional substitutions.

Where the additional substitution to the subtilisin 309 variant is at position 74 atone, the substitution is preferably with Asn, Asp, Glu, Gly, His, Lys, Phe or Pro. Particularly preferred is where the substitution is with Asp or His.

Where there is more than one additional substitution to the subfillisin 309 variant, preferred is where the additional substitutions occur at position 74 in combination with one or more of the following residues: 97, 99, 101, 102, 105 and 121. Preferred additional substitution combinations include the following: 74/97; 74/99; 74/101; 74/102; 74/105; 74/101; 74/97/901; 74/99/102; 74/101/102; 74/102/105; 74/97/101; 74/97/99/102; 74/97/101/102; 74/97/101/102/121; 74/97/99/101; 74/97/99/101; 74/97/99/101 102; 74/97/101/102/121 and/or 74/97/99/101/102/121. Most preferred additional substitution combinations include the following: 74/97; 74/102, 74/97/102, 74/101/102; 74/97/101/102; 74/97/101/102; 74/97/101/102; 74/97/101/102; 74/97/102 and 74/99/102.

Preferably, the additional substitutions to be made at each of the identified amino acid residue positions include but are not limited to substitutions at position 74 including Asp, His, Glu, Gly, Phe, Lys, Pro and

Asn; substitutions at position 97 including Asp, Thr, Asn, Gln, Gly and Ser, substitutions at position 99 including Gly, Asp, Lys, Leu, Ala, Glu and Ser, substitutions at position 101 including Gln, Thr, Asp, Glu, Tyr, Lys, Gly, Arg and Ser; substitutions at position 102 including Ser, Tyr, Ile, Leu, M, Ala, W, Asp, Thr, Gly and Val; substitutions at position 105 including Val, Leu, M, Tyr, Gly, Glu, Phe, Thr, Ser, Ala and Ile; and substitutions at position 121 including Asn, Thr, Ile and Ser. The specifically preferred amino acid(s) to be substituted at each such position are designated below in Table 2. Although specific amino acids are shown in Table 2, it should be understood that any amino acid may be substituted at the identified residues. As indicated herein before, these substitutions are in addition to the one or more substitutions at one or more of the loop regions, discussed above.

TABLE 2

	Amino Acid Residue	Preferred Amino Acid to be Substituted/Inserted
15	74	Asp, His
	97	Asp,Thr, Asn, Gly
	99	Arg, Gly, Asp, Lys, Leu, Ala, Glu
	101	Ala, Gin, Thr, Asp, Glu, Tyr, Lys, Gly, Arg
	102	lie, Tyr, Ser, Leu, Ala, Thr, Gly
20	105	Val, Leu, Tyr, Gly, Phe, Thr, Ser, Ala
	121	Ser, Thr, ile

Preparation of enzyme variants

Example 1

Mutant 309 DNA Sequences

A phagemid (pJMA602) containing the wild type subtilisin 309 (i.e., savinase) gene is constructed. The 2.8 Kbp Pvu II restriction enzyme fragment of plasmid pUC119, (Vieira, J. and Messing, J., "Production of Single-Stranded Plasmid DNA", 153 METHODS IN ENZYMOLOGY 3-11 (1989)) is cloned into the Pvu II site of plasmid pUB110 (Bacillus Genetic Stock Center, Columbus, OH 1E9). The pUC119-pUB110 hybrid plasmid is named pJMA601. Into the BamH I restriction site of pJMA601 is cloned the polymerase chain reation-amplified 309 (savinase) gene from Bacillus lentus chromosomal DNA (National Collections of Industrial and Marine Bacteria Bacillus lentus 10309) giving phagemid pJMA602. Phagemid pJMA602 is transformed into Escherichia coll ung-strain CJ236 and a single stranded uracil-containing DNA template is produced using the VCSM13 helper phage (Kunkel, T.A., J.D. Roberts and R.A. Zakour, "Rapid and efficient site-specific mutagenesis

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without phenotypic selection", METHODS IN ENZYMOLOGY, Vol. 154, pp. 367-382, (1987); as modified by Yuckenberg, P.D. F. Witney, J. Geisselsoder and J. McClary, "Site-directed in vitro mutagenesis using uracit-containing DNA and phagemid vectors", Directed Mutagenesis - A Practical Approach, ed. M.J. McPherson, pp. 27-48, (1991); both of which are incorporated herein by reference). A single primer site-directed mutagenesis modification of the method of Zoller and Smith (Zoller, M.J., and M. Smith, "Oligonucleotidedirected mutagenesis using M13-derived vectors; an efficient and general procedure for the production of point mutations in any fragment of DNA". NUCLEIC ACIDS RESEARCH, Vol. 10, op. 6487-6500, (1982), incorporated herein by reference) is used to produce all mutants (basically as presented by Yuckenberg, et al., 1991, above). Oligonucleotides are made using an Applied Biosystem Inc. 380B DNA synthesizer. Mutagenesis reaction products are transformed into Escherichia coli strain MM294 (American Type Culture Collection E. Coli, 33625). All mutants are confirmed by DNA sequencing and the isolated DNA is transformed into the Bacillus subtilis expression strain BG2036 (Yang, M. Y., E. Ferrari and D. J. Henner, (1984), "Cloning of the Neutral Protease Gene of Bacillus subtilis and the Use of the Cloned Gene to Create an In Vitro-derived Deletion Mutation", JOURNAL OF BACTERIOLOGY, Vol. 160, pp. 15-21). For some of the mutants a modified pJMA602 with a frameshift-stop codon mutation in the corresponding toop is used to produce the uracil template. Oligonucleofides are designed to restore the proper reading frame at position 203 and also encoded for random substitutions at positions 57, 58, 59, 60, 61, 63, 64, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 124, 125, 126, 127, 128, 129, 130, 131, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 181, 182, 183, 184, 185, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213 and 214 (equimolar and/or variable mixtures of all four nucleotides for all three bases at these codons). Mutations that correct for the frameshiftstop and produce a functional enzyme are identified by their ability to digest casein. The random substitutions are determined by DNA sequencing.

Example 2

Fermentation

The Bacillus subtilis cells (BG2036) containing a subtilisin mutant of interest are grown to mid-log phase in a one liter culture of LB-glucose broth and inoculated into a Biostat ED fermenter (B. Braun Biotech, Inc., Allentown, Pennsylvania) in a total volume of 10 liters. The fermentation media contains Yeast Extract, starch, antifoam, buffers and trace minerals (see FERMENTATION.

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A PRACTICAL APPROACH, Ed. B. McNeil and L. M. Harvey, 1990). The broth is kept at a constant pH of 7.0 during the fermentation run. Chloramphenical is added for antibiotic selection of mutagenized plasmid. The cells are grown overnight at 37°C to an Ason of about 60 and harvested.

Example 3 Purification

The fermentation broth is taken through the following steps to obtain pure enzyme. The broth is cleared of Bacillus subtilis cells by centrifugation, and clarified by removing fine particulates with a 100K cutoff membrane. This is followed by concentration on a 10K cutoff membrane, and flow dialysis to reduce the ionic strength and adjust the pH to 5.5 using 0.025M MES buffer (2-(N-morpholino)ethanesulfonic acid). The enzyme is further purified by loading it onto either a cation exchange chromatography column or an affinity adsorption chromatography column and eluting it from the column with a NaCl or a propylene glycol gradient (see Scopes, R. K., PROTEIN PURIFICATION PRINCIPLES AND PRACTICE, Springer-Verlag, New York (1984), incorporated herein by reference).

The pNA assay (DelMar, E.G., C. Largman, J.W. Brodrick and M.C. Geokas, ANAL. BIOCHEM., Vol. 99, pp. 316-320, (1979), incorporated herein by reference) is used to determine the active enzyme concentration for fractions collected during gradient elution. This assay measures the rate at which pnitroaniline is released as the enzyme hydrolyzes the soluble synthetic substrate, succinyl-alanine-alanine-profine-phenylalanine-p-nitroanilide (sAAPF-pNA). The rate of production of yellow color from the hydrolysis reaction is measured at 410 nm on a spectrophotometer and is proportional to the active enzyme concentration. In addition, absorbance measurements at 280 nm are used to determine the total protein concentration. The active enzyme/total-protein ratio gives the enzyme purity, and is used to identify fractions to be pooled for the stock solution.

To avoid autolysis of the enzyme during storage, an equal weight of propylene glycol is added to the pooled fractions obtained from the chromatography column. Upon completion of the purification procedure the purity of the stock enzyme solution is checked with SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) and the absolute enzyme concentration is determined via an active site titration method using trypsin inhibitor type II-T; turkey egg white purchased from Sigma Chemical Compeny (St. Louis, Missouri). The measured conversion factors will show which changes made in the enzyme molecule at the various positions result in the

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enzyme variant having increased activity over the wild-type, against the soluble substrate pNA.

In preparation for use, the enzyme stock solution is eluted through a Sephadex-G25 (Pharmacia, Piscataway, New Jersey) size exclusion column to remove the propylene glycol and exchange the buffer. The MES buffer in the enzyme stock solution is exchanged for 0.1 M Tris buffer (Tris(hydroxymethyl-aminomethane) containing 0.01M CaCl₂ and pH adjusted to 8.6 with HCl. All experiments are carried out at pH 8.6 in Tris buffer thermostated at 25°C.

Characterization of Enzyme Variants

Example 4

Model Surface Preparation

Aminopropyl controlled pore glass (CPG) purchased from CPG Inc. (Fairfield, New Jersey) is used as a support for covalently attaching the sAAPF-pNA substrate purchased from Bachem, Inc. (Torrence, California). The reaction is carried out in dimethyl sulfoxide and (1-ethyl-3-[3-(dimethylamino)propyl] carbodilimide hydrochloride) (EDC) is used as a coupling agent. Upon completion (monitored by pNA assay), the excess solvent is removed, and the CPG:sAAPF-pNA is rinsed with dimethyl sulfoxide (DMSO) and doubly-distilled water. This is followed by oven drying with a N2 purge at about 70°C. The reaction scheme and preparation of the immobilitzed substrate are conducted as described by Brode, P.F. III, and D.S. Rauch, "Subtillisin BPN": Activity on an Immobilized Substrate," LANGMUR, Vol. 8, p. 1325-1329, (1992), incorporated herein by reference.

The CPG surface will have 62,000 \pm 7,000 pNA molecules/ μ m². The surface area will remain unchanged from the value of 50.0m²/g reported by CPG Inc. for the CPG as received. This suggests that the procedure used to add sAAPF-pNA to CPG does not damage the porous structure (mean diameter is 486 Å).

Example 5

Surface Hydrolysis Assay

Using CPG:sAAPF-pNA, adsorption of an enzyme variant and hydrolysis of a CPG-bound peptide can be measured in a single experiment. A small volume of enzyme variant stock solution is added to a flask containing Tris buffer and CPG:sAAPF-pNA which has been degassed. The flask is shaken on a wrist-action shaker for a period of 90 minutes during which the shaker is stopped at various time intervals (for example, every 2 minutes during the early stages of adsorption hydrolysis - e.g., the first 20 minutes - and every 10 minutes towards the end of the experiment). The CPG:sAAPF-

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pNA is allowed to settle and the solution is sampled. Both the experimental procedure and the calculation of the adsorption and hydrolysis are conducted as described by Brode et al., 1992, above.

All enzymes are monitored for stability against autolysis and should show no appreciable autolytic loss over the time course of this experiment. Therefore, enzyme adsorption can be determined by measuring solution depletion. The difference between the initial enzyme variant concentration and the concentration measured at each individual time point gives the amount of enzyme variant adsorbed. The amount of pNA hydrolyzed from the surface is measured by taking an absorbance reading on an aliquot of the sample at 410 nm. The total amount of pNA hydrolyzed is calculated by adding the amount sampled and the amount remaining in the flask. This value is corrected by subtracting the amount of pNA that is hydrolyzed by Tris buffer at pH 8.6 when no enzyme is present. This base-hydrolysis ranges from 7-29% of the total hydrolysis depending on the efficiency of the enzyme.

Example 6

Soluble Substrate Kinetic Analysis

The rates of hydrolysis of the soluble substrate sAAPF-pNA are monitored by measuring the adsorbance increase as a function of time at 410 nm on a DU-70 spectrophotometer. The enzyme concentration is held constant and is prepared to be in the range of 6-10 nanomolar while the substrate concentration is varied from 90-700 μM sAAPF-pNA for each kinetic determination. An adsorbance data point is taken each second over a period of 900 seconds and the data are transferred to a LOTUS™ spreadsheet (Lotus Development Corporation, Cambridge, Massachusetts). Analysis for kinetic parameters is conducted by the standard Lineweaver Burk analysis in which the data in the initial part of the run (generally the first minute) are fit to a linear regression curve to give v₀. The v₀ and s₀ data are plotted in the standard inverse fashion to give K_M and k_{Cat}.

30 F. Example Subtilisin 309 Variants

Subtilisin 309 variants of the present invention which have decreased adsorption to and increased hydrolysis of surface bound substrates are exemplified in Tables 3-38, below. In describing the specific mutations, the original amino acid occurring in wild-type is given first, the position number second and the substituted amino acid third.

TABLE 3

	Gin57Asp
	Gln57Glu
	Gln57Ser
	Asp58Glu
5	Gly59Asn
	Gly59Asp
	Gly59Gln
	Gly59Glu
	Gly59Pro
10	Gly59Ser
	Asn60Asp
	Asn60Gln
	Asn60Glu
	Asn60Ser
15	Gly61Asn
	Gly61Asp
	Gly61Gln
	Gly61Glu
	Gly61Pro
20	Gly615er
	Gly63Asn
	Gly63Asp
	Gly63Gln
	Gly63Glu
25	Gly63Pro
	Gly63Ser
	Thr64Asn
	Thr64Asp
	Thr64Gln
30	Thr64Glu
	Thr64Gly
	Thr64Pro
***************************************	Thr64Ser
35	TABLE 4
33	
***************************************	Loop 1 - Double Mutation Variants
	Gln575er + Asn60Glu
	Asp58Glu + Gly8lGln
	Gly59Ser + Gly63Ser
40	Asn60Ser + Gly61Ser
	Gly63Asn + Thr64Asp
	Gly59Asn + Thr64Glu
	Asn60Glu + Gly63Ser
	Asn60Gln + Gly63Gln
45	Asn60Asp + Gly63Ser
	Asp58Glu + Gly63Gln
	Gin57Asp + Thr64Gly
	Gln57Glv + Gly63Gln
	Asn60Glu + Gly63Asn
50	Gly61Gln + Gly63Asn
	Asp58Glu + Gly59Asn

Asp58Glu + Gly59Asn Asp58Glu + Thr64Pro

40	Gin57Ser + Gly59Asn + Gly63Pro
	Loop 1 - Triple Mutation Variants Gly59Pro + Gly63Gin + Thr64Glu
***************************************	TABLE 5
	TADICE
	arnaran + Ashouasp
35	Ashbugin + Giy63Pro Gln57Asn + Ash60Asp
	Gly59Ser + Thr64Glu Asn60Gln + Gly63Pro
	Gln57Glu + Gly63Pro
	Gly59Ser + Thr64Asp
30	Gly61Ser + Thr64Asp
200	Gly59Glu + Gly63Asn
	Asp58Glu + Gly63Ser
	Gln57Glu + Gly61Gln
	Gly61Gln + Thr64Glu
25	Gly59Asn + Asn60Glu
	Asp58Glu + Gly61Asn
	Gln57Asp + Gly63Gln
	Gln57Glu + Gly61Ser
	Gln57Asp + Gly59Pro
20	Gln57Glu + Gly59Gln
	Gly63Gln + Thr64Asn
	Gly59Asp + Gly63Asn
	Gly61Pro + Gly63Ser
	Asn60Gln + Gly61Ser
15	Gly59Glu + Gly63Pro
	Gln57Asp + Gly61Asn
	Glv6lSer + Thr64Asn
	Gln57Asn + Gly61Ser
***	Gly59Glu + Gly63Ser
10	AsneOAsp + Thre4Gln
	Asp58Glu + Thr64Ser
	Gly61Asn + Thr64Gln
	Gln57Asn + Gly59Glu` Asn60Glu + Gly61Pro
3	Asp58Glu + Asn60Ser
5	Asn60Asp + Gly61Gln
	Asn60Glu + Gly63Gln
	Asp58Glu + Gly61Pro

GlyS9Pro + Gly63Gin + Thr64Glu Gln57Ser + Gly53Pan + Gly63Pro Gly59Pro + Asn60Asp + Thr64Asn Gln57Glu + Gly59Psan + Gly63Pro Gln57Asp + Gly63Pro + Thr64Asn Gln57Asp + Gly63Pro + Thr64Asn Gln57Aser + Asn60Glu + Thr64Gly 45 Gln57Ser + Asn60Glu + Thr64Gly Gln57Ser + Asn60Ser + Gly63Ser Gly61Ser + Gly63Ser + Thr64Gly Asp58Glu + Gly63Pro + Thr64Gly Gln57Asn + Asp58Glu + Gly61Pro 50 Asp58Glu + Gly63Pro + Thr64Pro Gln57Asn + Gly59Glu + Gly61Ser Gly59Glu + Gly61Ser Gly5Glu + Gly61Ser

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Gln57Asp + Asn60Gln + Thr64Gly
                  Asn60Glu + Gly61Gln + Thr64Gly
                  Gln57Asp + Gly59Pro + Gly63Pro
                  Gln57Asn + Glv63Asn + Thr64Glv
5
                  Gln57Ser + Gly59Asp + Gly61Ser
                  Gly61Gln + Gly63Asn + Thr64Pro
                  Gln57Glu + Gly59Pro + Thr64Ser
                  Asn60Asp + Glv63Gln + Thr64Glv
                  Asp58Glu + Gly63Asn + Thr64Gln
                  Asp58Glu + Gly61Gln + Gly63Gln
10
                  Gln57Asp + Gly61Pro + Thr64Gln
                  Asp58Glu + Gly59Asn + Gly61Ser
                  Asp58Glu + Gly59Ser + Asn60Ser
                  Gln57Asn + Gly61Pro + Thr64Gly
                  Gly59Glu + Gly61Pro + Gly63Pro
15
                  Gly59Glu + Gly61Gln + Gly63Asn
                  Glv59Glu + Glv61Pro + Glv63Gln
                  Glv59Glu + Glv61Pro + Thr64Asn
                  Gln57Asn + Asp58Glu + Thr64Gln
```

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TABLE 6

```
Loop 1 - Quadruple Mutation Variants
             Gly59Gln + Asn60Asp + Gly61Pro + Gly63Pro
             Gly59Ser + Asn60Gln + Gly63Ser + Thr64Asp
             Glv59Pro + Asn60Ser + Glv61Ser + Glv63Gln
25
             Gln57Glu + Glv59Pro + Asn60Ser + Gly61Pro
             Gln57Glu + Asn60Gln + Gly63Asn + Thr64Gly
             Gln57Ser + Gly59Ser + Asn60Asp + Gly61Ser
             Gln57Ser + Asn60Glu + Gly61Fro + Thr64Pro
             Asn60Gln + Glv61Pro + Glv63Gln + Thr64Asp
30
             Asn60Glu + Gly61Gln + Gly63Asn + Thr64Pro
             Gln57Glu + Gly59Gln + Gly61Pro + Thr64Gln
             Gln57Asn + Asp58Glu + Gly59Ser + Asn60Gln
             Asp$8Glu + Asn60Ser + Gly63Ser + Thr64Ser
             Gln57Glu + Gly59Pro + Gly63Gln + Thr64Ser
35
             Asp58Glu + Gly59Ser + Asn60Ser + Gly63Ser
             Gly59Asn + Asn60Asp + Gly61Ser + Thr64Gln
             Gln57Glu + Asp58Glu + Gly59Gln + Gly61Gln
             Gln57Glu + Asp58Glu + Asn60Ser + Thr64Pro
40
             Gln57Asp + Asp58Glu + Gly61Ser + Gly63Pro
             Gln57Asp + Asp58Glu + Asn60Gln + Gly61Gln
             Gln57Ser + Asp58Glu + Gly59Glu + Asn60Gln
             Asp58Glu + Glv59Asp + Gly61Ser + Gly63Gln
             Gly59Glu + Asn60Asp + Gly61Asn + Gly63Asn
45
             Glv59Asp + Asn60Asp + Gly61Asn + Gly63Gln
             Gly59Glu + Asn60Asp + Gly61Pro + Thr64Ser
             Asp58Glu + Gly59Glu + Asn60Asp + Thr64Gly
             Asp58Glu + Gly59Glu + Asn60Asp + Gly61Pro
             Asp58Glu + Gly59Glu + Asn60Glu + Gly61Asn
```

TABLE 7

1/	IABLE /		
	e Mutation Variants		
Va.	93Ala		
Val	L 93Asn		
5 Val	93Asp		
Va.	1 93Cys		
	1 93Gln		
Va.	l 93Glu		
	93Gly		
	L 93His		
Val	L 93Met		
	93Pro		
Va:	1 93Ser		
	93Thr		
	1 94Ala		
	J 94Asn		
	94Asp		
	1 94Cys		
	1 94Cys 1 94Gln		
	1 94Glu		
	1 94Gly		
	1 94019 1 94His		
	1 9411e		
	1 94Met		
	1 94Pro		
	1 94710 1 948er		
	1 945er 1 94Thr		
	1 94Val		
	v 95Asn		
	y 95Asp		
	y 95Gln y 95Glu		
	y 95910 y 959ro		
	y 95Ser		
	y soser a 96Asn		
	a 96Asp		
	a 96Gln		
	a 96Glu		
	a 96Gly		
	a 96His		
	a 96Pro		
	a 96Ser		
	a 96Thr		
	r 97Asp		
	r 97Glu v 98Asn		
	y 98Asp		
	y 98Gln		
	y 98Glu		
	y 98Pro		
	y 98Ser		
	r 99Asp		
Se	r 99Glu		

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	26	
	Gly100Asn	
	Gly100Asp	
	Gly100Gln	
	G1y100G1u	
5	Glv100Pro	
	Glv100Ser	
	Ser101Asp	
	Serl01Glu	
	Val102Ala	
10	Val102Asn	
	Val102Asp	
	Val102Cvs	
	Val102Gĺn	
	Vall02Glu	
15	Vall02Gly	
	Vall02His	
	Val102Met	
	Val102Pro	
	Val102Ser	
20	Vall02Thr	
	Serî03Asp	
	Serl03Glu	
	Ser104Asp	
	Ser104Glu	
25	Ile105Ala	
	Ile105Asn	
	Ile105Asp	
	Ile105Cys	
	Ilel05Gln	
30	Ile105Glu	
	Ile105Gly	
	Ile105His	
	Ile105Leu	
	Ile105Met	
35	Ile105Pro	
	Ile105Ser	
	Ile105Thr	
***************************************	Ile105Val	
40	TABLE 8	
	Loop 2 - Double Mutation Variants	
***************************************	Val 93Gln + Ser 99Glu	
	Gly 95Ser + Gly 98Gln	
	Ser101Asp + Ile105Ala	

	Loop 2 - Double Mutation Variants
	Val 93Gln + Ser 99Glu
	Gly 95Ser + Gly 98Gln
	Ser101Asp + Ile105Ala
45	Leu 94Ser + Gly 95Ser
	Leu 94Pro + Ser10lAsp
	Gly 98Gln + Serl03Asp
	Ser 97Asp + Tyrl02Gln
	Tyrl02Cys + Ile105Met
50	Val 93Pro + Gly 96Gln
	Ser 99Glu + Gly100Pro
	SerioBash + HeloSLen

	Ser 97Asp + Gly 98Gln
	Val 93Ser + Ser 99Asp
	Leu 94Ser + Gly 98Glu
	Glv 95Glu + Tyr102Met
5	Gly 95Asn + Ser103Glu
	Glv 98Ser + Tvrl02Thr
	Glv 98Gln + Tyr102Cvs
	Leu 941le + 11e105Gln
	Leu 94Asp + Gly100Gln
10	Ala 96Gly + Ser101Asp
	Ser101Glu + Ile105Gln
	Gly 95Gln + Ile105Ser
	Val 93Gln + Glyl00Pro
	Val 93Met + Ser104Asp
12	
15	Gly 98Pro + Ser101Asp
	Val 93Pro + Ile105His
	Gly 95Asp + Gly100Ser
	Tyr102Cys + Ile105Leu
	Gly100Asn + Ile105Met
20	Gly 98Asn + Ser101Glu
	Ser 99Glu + Ile105Gln
	Val 93Thr + Tyr102Thr
	Gly 98Ser + Ser104Glu
	Gly 95Asn + Ser104Glu
25	Val 93Pro + Ser103Glu
	Gly 95Asn + Tyrl02Ile
	Leu 94Pro + Gly 98Asp
	Leu 94His + Gly 98Asp
	Val 93Asn + Tyrl02Thr
30	Tyr102Ala + Ser103Asp
	Gly 98Pro + Serl03Glu
	Leu 94Cvs + Tvrl02Leu
	Val 93Gly + Gly 98Ser
	Glv100Gln + Tyr102Ser
35	Val 93Thr + Gly100Asn
0.00	Gly 98Asn + IlelO5Pro
	Val 93Asp + Leu 94Ala
	Leu 94Gly + Ser104Glu
	Val 93Met + SeriOlAsp
40	Val 93Met + Ser 97Glu
40	Ala 96Pro + Ile105Asn
	Ser 97Glu + Gly 98Pro
	Ala 96Thr + Ser 99Glu
	Val 93Asn + Gly100Asn
45	Gly 95Gln + Gly 98Pro
	Gly 95Asn + Ala 96His
	Val 93Ser + Ser103Asp
	Gly 98Gln + Ilel05Pro
	Val 93Cys + Ilel05Glu

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	TABLE 9
	Loop 2 - Triple Mutation Variants
	Val 93Gln + Leu 94Thr + Ser 99Glu
	Leu 94Met + Gly 95Gln + Ser104Asp
5	Ser 99Glu + TyrlO2Met + IlelO5Thr
	Val 93Thr + Leu 94Thr + Ile105Cys
	Leu 94Asp + Ala 96Thr + Gly 98Asn
	Val 93Met + Gly 95Gln + Ser103Asp
	Val 93Cys + Ala 96Pro + Ser 99Glu
10	Leu 94Asp + Ala 96Gly + Gly100Gln
	Leu 94His + Gly 98Gln + Ser 99Glu
	Gly 95Pro + SerlölAsp + Tyrlö2Gln
	Leu 94Asn + Gly 95Gln + Ser101Asp
	Leu 94His + Gly 98Pro + Ser104Glu
15	Leu 94Thr + Ala 96Asn + Gly100Pro
	Gly 95Ser + Gly 98Ser + Tyr102Glu
	Ala 96Thr + Ser 97Asp + Tyrl02Thr
	Leu 94Asn + Gly100Ser + Ser101Glu
	Leu 94Met + Gly 98Gln + Gly100Asn
20	Val 93Pro + Ala 96Glu + Ile105Ala
	Val 93Cys + Gly 95Glu + Tyr102Leu
	Leu 94Cys + Gly 95Ser + Ser 97Asp
	Gly 95Gln + Ser101Glu + Tyr102His
	Val 93Gln + Gly 95Glu + Ile105Gln
25	Val 93Gly + Ser 99Asp + Ile105Gly
	Gly 95Asn + Gly 98Glu + Ile105Val
	Ser 97Glu + Gly 98Pro + Tyr102Thr
	Val 93Glu + Leu 94Ile + Gly100Gln
30	Ala 96Pro + Ser101Asp + Ile105Pro
20	Gly 98Pro + Ser103Asp + Ile105Val Ala 96Gln + Ser 99Asp + Tyr102Ser
	Ser 97Asp + Gly 98Ser + Ile105Asn
	Val 93Gln + Gly 98Asn + Tyr102Leu
	Leu 94Glv + Tyr102Pro + Ser103Glu
35	Val 93Thr + Gly100Gln + Ser104Glu
32	Val 93Gly + Gly100Gln + Ser103Glu
	Ala 96Thr + Gly100Ser + Ser103Glu
	Glvl00Asn + Serl01Glu + Ile105Thr
	Gly 95Asp + Tyrl02Gly + Ile105Met
40	Val 93Cys + Ala 96Thr + Ile105Cys
40	Ala 96Gly + Gly 98Asp + Ser 99Asp
	Gly 95Ser + Ser 97Asp + Gly 98Asp
	Leu 94Asn + Ser103Glu + Ser104Asp
	Tyr102Val + Ser103Glu + Ser104Glu
45	Ser 99Asp + Gly100Glu + Ile105Met
40	Ser 97Asp + Gly 98Asp + Ser 99Glu
	Gly 95Asn + Ser101Glu + Ser103Glu
	SerlOlGlu + TyrlO2Asn + SerlO3Glu
	Leu 94Asp + Ser 99Glu + Gly109Gln
50	Gly100Asp + Ser101Glu + Ser104Glu
30	Leu 94Asp + Gly 98Glu + Ile105Cys
	Gly 95Glu + Ser 97Glu + Tyr102Asn
	Tyr102Thr + Ser103Glu + Ile105Glu
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```
Gly 95Asp + Ser 99Glu + Gly100Gln
Gly 95Glu + Ser 99Glu + Tyr102Met
Val 93Gln + Ser 97Asp + Ser 99Glu
Gly100Glu + Ser101Asp + Ser103Asp
Val 93Asp + Ser103Glu + Ser104Glu
Val 93Asp + Ser 99Asp > Gly100Asp
Ala 96Gln + Gly100Asp + Ser104Asp
Val 93Asp + Ser101Glu + Ile105Asp
Leu 94Asp + Ser 99Glu + Ser101Glu
```

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TABLE 10

```
Loop 2 - Quadruple Mutation Variants
           Leu 94Asn + Ser 97Glu + Tyrl02Asn + Ile105Met
           Leu 94Pro + Gly 95Glu + Gly100Gln + Tyr102Ala
15
          Val 93Cvs + Leu 94Met + Glv 95Pro + Ala 96Gln
          Gly 95Pro + Ser 97Glu + Tyrl02Gln + Ile105Leu
          Gly 95Asp + Gly100Pro + Tyr102Val + Ile105Cys
          Ala 96Thr + Gly100Asp + Tyr102Ala + Ile105Asn
          Val 93Asn + Leu 94Cys + Ser101Asp + Tyr102Val
20
          Val 93Asn + Gly 95Asn + Ser104Asp + Ile105Val
          Leu 94Ser + Gly 98Pro + Ser103Glu + Ile105Val
          Val 93Asn + Leu 94His + Gly 95Asn + Ile105Asn
          Ala 96Ser + Gly 98Asn + Ser 99Glu + Tvr102Glv
          Val 93Asn + Gly 98Asn + Tyr102Ile + Ile105Asp
          Val 93Asn + Tyr102Asn + Ser103Asp + Ile105Ser
25
          Ala 96Ser + Gly100Ser + Ser101Asp + Tyr102Pro
          Leu 94Pro + Ala 96Ser + Ser101Asp + Tyr102Ser
          Val 93Met + Ala 96Thr + Ser104Asp + Ile105Gln
          Val 93Met + Leu 94Ala + Glv 95Pro + Ser104Glu
30
          Val 93Cys + Gly 95Pro + Ala 96Glu + Tyr102Val
          Gly 95Asn + Ala 96Asn + Ser104Glu + Ile105Pro
          Val 93Asn + Leu 94Asn + Glv 98Glu + Ser 99Glu
          Leu 94His + Gly 98Glu + Ser 99Glu + Tyr102Ser
          Gly 95Pro + Gly 98Glu + Ser 99Asp + Ile105Gly
35
          Val 93Ala + Ala 96Ser + Ser103Glu + Ser104Glu
          Leu 94Gly + Ser 97Asp + Gly 98Asp + Ser 99Glu
          Val 93Cys + Leu 94Asp + Gly 95Asn + Gly100Glu
          Val 93Ser + Ser101Glu + Ser103Asp + Ser104Asp
          Ala 96Ser + Ser101Glu + Tyr102Gln + Ser103Asp
40
          Val 93Thr + Gly100Asn + Ser101Glu + Ser103Asp
          Val 93Asn + Leu 94Glu + Gly 95Glu + Ser 99Glu
          Leu 94Asp + Ala 96Gly + Ser 99Glu + Ile105Cys
          Leu 94Ala + SerlOlGlu + SerlO4Asp + Ile105Ser
          Ala 96His + Ser101Glu + Ser104Glu + Ile105Ala
45
          Val 93Glv + Glv100Pro + Serl01Glu + Serl04Asp
          Gly 95Gln + Ser101Glu + Ser104Asp + Ile105Met
          Gly 98Gln + SerlOlGlu + SerlO4Glu + Ile105Asn
          Val 93Gly + Ser101Asp + Tyr102Glu + Ile105Asp
          SerlOlAsp + Tyr102Val + SerlO4Glu + Ile105Glu
50
          Val 93Cvs + Glv 95Asp + Glv 98Asp + Glv100Pro
          Gly 95Asp + Ser 97Glu + Tyrl02Ala + Ile105Cys
          Val 93Thr + Gly 95Glu + Ala 96Asn + Ser 99Asn
```

	Val	93Cvs	÷	Glv 95Asp	4	Ser 99Glu	+	Ile105Val
	Val	93CVs	+	Ser101Asp	+	Ser103Glu	÷	Ile105Asp
	Ala	96His	÷	Ser 97Glu	+	Ser 99Asp	÷	Ile105Asn
						Ser 99Glu		
5						Ser 99Asp		
						Gly 98Gln		
						Ser 99Glu		
	Val	93Met	4	Glv100Asp	4	Tvr102Asp	4-	Ser103Asp
	Leu	9461v	4	Ser101Asp	4	Tyr102Ala	·ŧ	Ile105Glu
10	Ser	97Glu	+	Gly 98Asp	+	Gly100Asp	+	Tyr102Gly
						Gly100Glu		
						Gly100Glu		
						Gly100Asp		
						Ser 99Asp		
15						Ser 99Glu		
						Ser 99Asp		
						Tyr102Asn		
								Ser103Asp
						Ser 99Asp		
20						Tyr102Pro		
		****************					*****	

TABLE 11

	Loop 3 - Single Mutation Variants	
***************************************	Leul24Ala	
25	Leu124Asn	
	Leu124Asp	
	Leu124Cys	
	Leu124Gln	
	Leu124Glu	
30	Leu124Gly	
	Leul24His	
	Leu124Ile	
	Leu124Met	
	Leu124Pro	
35	Leu124Ser	
	Leu124Thr	
	Leu124Val	
	Gly125Asn	
	Gly125Asp	
40	Gly125Gln	
	Gly125Glu	
	Gly125Pro	
	Gly1259er	
	Serl26Asp	
45	Ser126Glu	
	Pro127Asn	
	Pro127Asp	
	Pro127Gln	
	Pro127Glu	
50	Pro127Gly	
	Pro127Ser	
	Ser128Asp	

	Ser128Glu
	Pro129Asn
	Pro129Asp
	Pro129Gln
5	Pro129Glu
,	Pro129Gly
	Pro129Ser
	Ser139Asp
	Serl30Glu
	Alal31Asn
10	Alal31Asp
	Alal3lGln
	Alai3iGlu
	Alai3iGly
15	Ala131His
	Ala131Pro
	Ala131Ser
	Ala131Thr
	W. V. V. V. V.
20	TABLE 12
	Loop 3 - Double Mutation Variants
3400000	Leu124Gln + Ser128Glu
	Gly125Ser + Ser126Glu
	Gly125Ser + Ser128Glu
25	Pro127Glv + Ser130Glu
	Leul24Thr + Serl26Glu
	Serl26Glu + Prol29Ser
	Gly125Gln + Ser128Glu
	Pro127Ser + Ser130Glu
30	Glv125Glu + Pro127Asn
20	Pro129Gln + Seri30Glu
	Gly125Asp + Ala131His
	Pro127Glv + Ala131Glu
	Leu124His + Ser126Asp
35	Pro127Gly + Pro129Asp
20	Ser126Glu + Ala131Gln
	Leu124Asp + Ala131Pro
	Glv125Pro + Pro127Glu
	Glyl25Ser + Serl26Asp
40	Leu124Gln + Ala131Asn
40	Glyl25Asp + Prol29Ser
	Pro129Asn + Ala131Asp
	Pro127Asn + Ser128Asp
	Prol29Gly + Ala131Glu
45	Pro127Ser + Pro129Asp
40	Pro127Ser + Ser126Glu
	Leu124Gly + Ser130Glu
	Glyl25Asn + Serl30Glu
	Leu124Glu + Pro127Asn
	Seri30Glu + Ala131Gly
50	
	Ser130Asp + Ala131Thr
	Leul24Gln + Serl28Asp

Leu124Gln + Ser128Asp

	Leu124Ser + Ala131Pro
	Prol29Ser + Ser130Glu
	Gly125Gln + Pro127Asp
	Leu124Cys + Alal31Thr
5	Gly125Gln + Prol29Gln
	Leul24Met + Alal31Gln
	Gly125Gln + Alal31Asp
	Ser128Glu + Ala131Asn
	Serl30Glu + Ala131Pro
10	Gly125Pro + Ala131Ser
	Prol27Ser + Prol29Asn
	Ser126Glu + Pro127Gln
	Pro127Ser + Serl30Asp
	Pro127Gly + Ser128Asp
15	Glv125Glu + Pro127Ser
-	Leul24Cys + Prol29Asn
	Gly125Gln + Pro129Glu
	Gly125Asn + Alal31Asp
	Gly125Ser + Prol29Gln
20	Ser126Asp + Pro129Gln
	Leul24Val + Prol29Asn
	Leul24His + Serl26Glu
	Pro127Glu + Alal31Gly
	Leu124Thr + Gly125Pro
25	Leu124His + Serl30Glu
	Gly125Asn + Ser126Asp
	Prol29Asn + Ala131Pro
	Pro127Gln + Pro129Asn
	Leul24Gly + Prol29Glu
30	
	TABLE 13
	Loop 3 - Triple Mutation Variants
***************************************	Glv125Gln + Ser126Gln + Ala131His
	Ser126Asp + Pro127Ser + Ala131His
35	Leu124Val + Ser130Asp + Ala131Asn
33	Leul24Gln + Serl26Glu + Alal31Ser
	Gly125ser + Pro129Glu + Ala131Gly
	Leu124Ser + Pro127Asp + Ala131Gln
	Pro127Ser + Ser129Asp + Ala131His
40	Leui24Thr + Pro127Glu + Ale131Ser
40	Leul24Gln + Ser126Glu + Ala131Asn
	Gly125Asn + Pro127Glu + Ala131Gln
	Gly125Gln + Ser126Asp + Pro127Gln
	Pro127Asn + Ser130Asp + Ala131Thr
45	Gly125Asn + Prol27Glu + Prol29Asn
4.5	Gry125ASh + Frode / Gru + Frode / Frod

Leu124Thr + Ser128Asp + Ala131Gln Gly125Ser + Pro129Gln + Ale131Glu Pro127Gln + Pro129Asn + Ser130Glu Leu124Tle + Gly125Gln + Ser130Glu Pro129Asn + Ser130Glu + Ala131Gly

Leu124Ser + Gly125Ser + Pro129Gln Leu124Asn + Gly125Gln + Ser128Asp WO 95/30011 PCT/US95/04768

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			Pro127Ser		
	Gly125Ser	ź	Pro127Ser	÷	Ala131Asp
	Gly125Ser	+	Ser128Glu	+	Pro129Gln
	Pro127Asn	÷	Ser128Asp	+	Ala131Gly
5			Gly125Ser		
	Gly125Gln	+	Pro129Ser	4	Ser130Asp
	Gly125Pro	÷	Ser126Glu	÷	Pro129Asn
	Pro129Gly	+	Ser130Asp	+	Ala131Pro
	Glv125Asn	÷	Ser126Asp	÷	Prol29Glv
3	Gly125Asp	4	Ser126Asp	+	Ala131Asn
			Serl26Glu		
			Ser126Asp		
			Serl28Glu		
			Prol29Glu		
			Ser128Glu		
			Serl28Glu		
			Ser128Asp		
			Ser128Glu		
			Pro127Asp		
			Pro127Glu		
			Ser126Asp		
			Pro127Glu		
			Ser128Asp		
			Ser128Glu		
			Ser128Asp		
			Pro127Glu		
			Ser130Asp		
			Pro129Glu		
			Pro127Glu		
)			Prol27Asp		
			Ser130Asp		
			Glv125Asp		
			Serl26Asp		
			Ser128Asp		
ş			Ser126Glu		
			Ser128Glu		
			Ser126Glu		
			Ser128Glu		
			Ser126Glu		
0			Pro129Ser		
	occasorop	<u> </u>			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

TABLE 14

	Leul24His	+	Gly125Ser	+	Prol29Gly	+	Alai31Asn
	Leu124Ala	4	Gly125Glu	4-	Prol27Gln	÷	Pro129Gln
	Leu124Ser	-ŧ-	Gly125Glu	÷	Ser126Asp	÷	Prol29Ser
	G1v125Glu	+	Serl26Glu	+	Pro127Gin	+	Ala131His
S	Leul 24Met	+	Gly125Asp	÷	Ser126Asp	+	Pro127Asn
-	Laul 24Gln	4	Ser128Glu	-ş-	Prol29Asp	÷	Alal31Gln
	Leu 124Val	4	Ser128Glu	4	Pro129Glu	4	Alal31Asn
			Ser128Asp				
			Ser128Glu				
10			Serl26Glu				
810			Gly125Gln				
	THULL THE C	di.	Gly125Gln	*	Serl30aen	4	Alalalasan
	Ten 12 duic		Prol27Glu	à	Serl286lu		Alai319ic
	Denizatio	4	Pro127Asp	1.	Corlibbon	4	Proligacin
15			Ser126Glu				
13			Ser128Glu				
			Ser128Asp				
	GIYIZDPIO	*	Gly125Asp	*	F10123G10	4	Setioner
	LeuizaAsn	**	GIYIZDASP	*	Serizonsp	7	Protz/ASp
			Gly125Asp				
20	Leuizgasp	4-	Gly125Glu	*	Serizonsp	4	ALGINAGIA
	GIA152GID	4	Ser126Glu	4	Serizaciu	**	Ataistint
			Serl26Glu				
	Leul24Met	+	Gly125Pro	+	Ser126Asp	4	Seri28Giu
	Leul24Asn	+	Gly125Ser	+	Ser126Asp	4.	SerizaAsp
25			Serl26Glu				
	Leu124Cys	+	Ser126Asp	*	SerizeGiu	4	ProizeGiu
	Serl26Asp	4	Pro127Asp	+	Pro129Glu	*	Alaisiser
	Gly125Asn	÷	Ser126Glu	+	Pro127GIu	*	Pro129G1u
	Leul24Ser	+	Ser126Asp	+	Pro12/Asp	*	Proligasp
30	Gly125Asp	+	Ser126Glu	4	Ser128Asp	÷	Pro129Ser
	Leu124Val	+	Gly125Asp	+	Ser126Glu	÷	Ser128Glu
	Gly125Glu	*	Ser126Glu	+	Serl28Asp	ተ	Pro129Asn
	Gly125Glu	4	Ser126Asp	÷	Prol27Ser	4	Ser128Asp
			Ser128Glu				
35	Leu124Cys	4	Ser128Glu	÷	Prol29Ser	4	Serl30Asp
	Gly125Gln	4	Ser128Glu	4	Ser130Glu	+	Alal3lHis
	Leu124Met	4	Prol27Gln	+	Serl28Glu	+	Ser130Glu
	Leu124Gly	+	Ser126Asp	+	Pro129Glu	4.	Ser130Asp
	Gly125Asn	÷	Ser126Glu	+	Prol29Glu	+	Serl30Glu
40	Leul24Gly	+	Gly125Asp	÷	Pro127Asp	÷	Prol29Gly
	Serl26Asp	÷	Ser128Asp	+	Serl30Glu	*	Alai3iGln
	Gly125Pro	÷	Ser126Asp	÷	Serl28Glu	4	Ser130Asp
	Ser126Asp	+	Prol27Gly	4	Serl28Glu	+	Ser130Glu
	Ser126Glu	+	Pro127Gly	÷	Serl28Asp	4	Serl30Glu
45	Ser126Asp	ŧ	Ser128Asp	÷	Prol29Ser	4	Serl30Asp
	Ser126Glu	9	Ser128Asp	÷	Serl30Asp	4-	Alal31His
	Ser126Glu	+	Ser128Glu	4	Ser130Glu	+	Alal31Ser
	Gly125Pro	÷	Ser126Glu	4	Ser128Glu	÷	Ser130Asp
	Leul24Val	4	Ser126Asp	4	Ser128Glu	÷	Ser130Asp
50	Gly125Gln	4	Ser126Glu	÷	Ser128Asp	+	Ser130Glu
	Ser126Glu	+	Ser128Asp	+	Pro129Gly	4	Ser130Glu
**************				****			***************************************

TABLE 15

	1ABLE 15
	Loop 4 - Single Mutation Variants
	Gly152Asn
	Gly152Asp
5	Gly152Gln
	Gly152Glu
	Gly152Pro
	Gly152Ser
	Ash153Asp
10	Asn153Gln
	Asnl53Glu
	Asnl53Ser
	Ser154Asp
	Ser154Glu
15	Gly155Asn
	Gly155Asp
	Gly155Gln
	Gly155Glu
	Gly155Pro
20	Gly155Ser
	Ala156Asn
	Ala156Asp
	Ala156Gln
	Ala156Glu
2.5	Ala156Gly
	Ala156His
	Ala156Pro
	Ala156Ser
	Ala156Thr
30	Gly157Asn
	Gly157Asp
	Gly157Gln
	Gly157Glu
35	Gly157Pro
23	Gly157Ser Ser158Asp
	Seri58Glu
	Ile159Ala
	Ilel59Asn
40	Ile159Asp
***	Ile159Cys
	Ile159Gln
	Ile159Glu
	Ile159Glv
45	Ilel59His
	Ile159Leu
	Ile159Met
	Ile159Pro
	Ile159Ser
50	Ile159Thr
	Ile159Val
	Ser160Asp
	Ser160Glu

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	Tyrl6lAla	
	Tyr16lAsn	
	Tyrl6lAsp	
	Tyrl6lCys	
5	Tyr161Gln	
	Tyr161Glu	
	Tyrl61Gly	
	Tyrl6lHis	
	Tyr161Ile	
10	Tvr161Leu	
	Tyr161Met	
	Tyr161Pro	
	Tyrl6lSer	
	Tyrl6lThr	
15	Tyrl61Val	
	TABLE 16	
	Loop 4 - Double Mutation Variants	
***************************************	······································	~~~~

	TABLE 10
	Loop 4 - Double Mutation Variants
	Seri54Glu + Gly155Asn
20	Ser154Asp + Gly157Gln
	Ser154Glu + Ile159His
	Gly152Gln + Gly157Asp
	Ser154Glu + Gly155Ser
	Asnl53Ser + Serl54Glu
25	Ala156Asn + Ser160Glu
	Alal56Thr + Serl58Glu
	Asnl53Glu + Glyl57Ser
	Gly155Asn + Ala156Asp
	Ile159Gly + Tyrl6lGly
30	Gly155Ser + Tyr16lGlu
	Ser154Asp + Gly155Pro
	Gly155Asp + Ala156Ser
	Gly152Glu + Asn153Ser
	Serl58Glu + Ile159Asn
35	Asn153Asp + Ala156His
	Ser154Glu + Tyr161Cys
	Ile159Leu + Tyr161Asn
	Gly157Asp + Ile159Gly
	Serl58Asp + Ile159Gly
40	Gly152Pro + Gly155Glu
	Gly155Gln + Serl60Asp
	Gly152Asp + Tyr16lMet
	Ser154Glu + Gly155Gln
	Gly155Glu + Tyr161Ala
45	Alal56Ser + Ser160Asp
	Alai56Glu + Tyrl6iLeu
	Gly152Pro + Gly157Asn
	Ser158Glu + Ile159Ser
	Gly157Asp + Tyrl6lThr
50	Serl58Asp + Ile159Cys
	Gly155Pro + Tyr161Ala
	Gly152Asp + Tyr16lAla

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	Alal56His	+	Ile159Asn
	Ser154Asp	4	Alal56His
	Gly157Pro	+	Serl58Asp
	Asn153Ser	4	Ilel59Cys
5	Ser154Asp	+	Alal56Ser
	Ser154Glu	÷	Tyr161Ala
	Ile159Leu	4	Tyr161Ala
	Gly152Glu	+	Gly155Gln
	Ala156Pro	÷	Gly157Glu
10	Asn153Asp	4	Tyrl61His
	Ala156Gln	+	Ile159Asn
	Gly152Pro	÷	Ser154Asp
	Gly155Gln		
	Ala156Ser	÷	Ile159Gly
15	Asn153Asp	÷	Gly157Gln
	Ile159Leu	÷	Serl 60Asp
	Gly155Glu	ş-	Ile159Gln
	Ser160Asp	4	Tyrl61Thr
	Ser158Asp	+	Ile159Gln
20	Ser154Glu	÷	Gly157Asn
	Ala156Gly	÷	Ile159His
	Ala156Ser	+	Serl58Asp
	Asn153Gln	÷	Gly155Glu
	Gly155Asn	÷	Ser158Glu
25	Ser158Glu	÷	Ile159Pro
	Ser158Asp	+	Ile159Leu

	Loop 4 - Triple Mutation Variants	
30	Ala156Asn + Gly157Asn + Tyr161Cys	
	Gly152Gln + Gly155Glu + Tyr161Asn	
	Gly152Gln + Asn153Gln + Ser154Glu	
	Gly155Ser + Ser158Glu + Tyr161Gln	
	Gly152Glu + Asn153Ser + Ala156Ser	
35	Glyl52Glu + Ilel59Pro + Tyr16lAsn	
	Gly152Asp + Gly157Gln + Tyr161Met	
	Gly155Asn + Ile159Thr + Tyr161His	
	Asn153Ser + Gly155Ser + Ser158Glu	
	Gly152Ser + Gly155Pro + Ser158Glu	
40	Gly152Pro + Gly157Gln + Ser160Asp	
	Gly152Gln + Ser154Asp + Tyr161Met	
	Ala156Pro + 11e159Asn + Tyr161Ile	
	Ilel59Asn + Serl60Glu + Tyrl61Ser	
	Gly152Asp + Hel59Ala + Tyr161Cys	
45	Asnl53Gln + Ilel59Ala + Ser160Glu	
	Asn153Asp + Gly155Prc + Tyr161Asn	
	Gly155Asn + Alal56Thr + Ser158Asp	
	Gly152Gln + Serl54Asp + Tyr161Gln	
	Gly157Ser + Serl58Asp + Tyr161Pro	
50	Ser154Glu + Gly155Ser + Ile159Cys	
	Gly155Gln + Ala156Asn + Ser158Asp	
	Gly155Asn + Gly157Asn + Ile159Ala	

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Gly157Asn + Ser158Glu + 1le159His Asn153Ser + 1le159Leu + Ser160Glu Ala156Gln + Gly157Asp + Tyr161Asn Gly155Asn + Ala156Glis + Tyr161Val Asn153Gln + Ala156Glis + Tyr161Val Ala156Glis + Ser160Glu + Tyr161Wis Ala156Glis + Ser160Glu + Tyr161Wis Ala156Gli + Ser160Asp + Tyr161Wis Ala156Gli + Ser160Asp + Tyr161Wis Ala156Gli + Ala156Gro + Tyr161Wis Ala15Gli + Ala156Gro + Tie159Ala Gly152Asp + Gly157Gli + Tle159Ala Gly152Asp + Ala156Fro + Tie159Ala Gly152Asp + Ala156Fro + Tyr161Cys Gly152Asp + Ala156Fro + Tyr161Cys Gly152Asp + Ala156Fro + Tyr161Cys Gly152Asp + Ala156Fro + Tyr161Asn Gly155Asp + Gly157Ser + Tyr161Asn Gly155Asp + Gly157Ser + Tyr161Asn Gly157Asn + Ser160Asp + Tyr161Asp Gly152Asp + Asn153Asp + Tyr161Met Gly152Asp + Asn153Asp + Tyr161Met Gly152Asp + Asn153Asp + Tyr161Met Gly152Asp + Gly155Asp Gly155Asp Ser154Asp + Gly155Asp Ser154Glu + Gly155Asp Ser154Glu + Gly155Asp Ser154Glu + Gly155Asp + Tyr161Met Gly155Asp + Ser156Glu + Gly155Asp Gly155Asp + Ala156Glu + Gly155Asp Gly155Asp + Ala156Glu + Gly155Asp Gly155Asp + Ala156Glu + Gly157Asp Ser156Asp + Ala156Glu + Gly157Asp Ser156Asp + Ala156Glu + Hel59Asn Gly155Asp + Ala156Glu + Hel59Asn Gly155Asp + Ala156Glu + Hel59Asn Gly155Asp + Ala156Glu + Gly157Asp Ser156Asp + Ala156Glu + Hel59Asn Gly155Asp + Ala156Glu + Gly155Asp + Ala156Glu + Gly155Asp + Ala156Glu + Gly155Asp + Ala156Glu + Gly155Asp + Gly15						
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40	Loc	Οį	o 4 - Quadrup	le	Mutation Vari	ani	ts	
***************************************	Alal56Pro +	}	Ile159Pro	+	Serl60Glu	+	Tyr161Thr	
	Asn153Gln +	4	Gly157Asn	÷	Ile159Gln	÷	Serl60Asp	
	Asn153Gln +	ŀ	Ala156Gly	÷	Gly157Glu	÷	Ile159Asn	
	Gly152Asn +	ŀ	Ile159Gln	4	Ser160Asp	4	Tyrl6lMet	
45	Gly152Pro +	F	Serl54Glu	4	Gly157Pro	+	Ile159Ala	
	Alal56Ser +							
	Asn153Ser +	į	Gly157Ser	4	Ile159Ala	÷	Serl60Asp	
	Gly155Gln +	ŀ	Ser158Asp	+	Ile159Gly	÷	Tyr161Met	
	Gly152Ser +	ļ.	Ser154Asp	+	Ala156Gln	÷	Ile159Cys	
50	Ala156His +	F	Gly157Pro	÷	Serl58Glu	÷	Tyrl61Met	
	Ala156Pro +	6	Gly157Asn	4	Ile159Met	+	Serl60Asp	
	Serl54Glu +	ŀ	Gly155Asn	+	Ile159Met	+	Tyr161Ala	

Gly152Ser + Ala156His + Gly157Pro + Ile159Gly Asn153Ser + Ile159Leu + Ser160Glu + Tyr161Thr Gly152Asn + Ser154Asp + Ala156Ser + Gly157Asn Ser154Asp + Gly155Gln + Ile159Leu + Tyr161Thr 5 Asn153Ser + Ser154Asp + Gly155Asn + Ile159Wet Gly152Asn + Asn153Gln + Gly155Asn + Ile159Wet Asn153Glu + Ser154Glu + Gly157Asn + Ile159Wet Asn153Glu + Ser154Glu + Gly157Asn + Ile159Wet Asn153Glu + Ser154Asp + Gly157Asn + Ile159Ser Gly152Ser + Gly157Asp + Ser158Asp + Ile159Ser Gly155Pro + Gly157Asp + Ser158Asp + Ile159Ser Ala156Glu + Gly157Asp + Ser158Asp + Ile159Ser Ser154Glu + Ala156Glu + Gly157Asp + Nala156Pro Ser154Glu + Ala156Glu + Gly157Asp + Ile159Asn Gly152Asn + Asn153Asp + Gly155Glu + Tyr161Gln Gly152Pro + Asn153Asp + Gly155Glu + Tyr161Gln Gly152Asp + Ala156Fro + Ile159Val + Ser160Asp Gly152Asp + Ala156Fro + Ile159Val + Ser160Asp Gly152Asp + Ala156Asp + Gly157Fon + Tyr161Cys Gly152Glu + Ser154Glu + Ile159Ala + Ser160Asp Gly152Asp + Ala156Asp + Gly157Fon + Ser158Asp Gly152Asp + Ala156Asp + Gly157Gln + Ser160Glu Ala156Thr + Ser154Asp + Gly157Gln + Ser160Glu Ala156Thr + Ser154Asp + Gly157Gln + Ser160Asp Gly152Asp + Asn153Asp + Ile159Leu + Ser160Glu Ala156Thr + Ser154Asp + Gly157Gln + Ser160Asp Gly152Asp + Ser154Glu + Ile159Mar + Ser160Glu Gly152Asp + Ser154Glu + Gly157Asp + Ser160Glu Ala156Thr + Ser154Asp + Gly157Gln + Ser160Asp Gly152Asp + Ser154Asp + Gly157Gln + Ser160Glu Gly152Asp + Ser154Asp + Gly157Gln + Ser160Glu Ala156Thr + Ser156Asp + Gly157Gln + Ser160Glu Ala156Glu + Ser154Asp + Gly157Gln + Ser160Glu Ala156Glu + Ser154Asp + Gly157Gln + Ser160Glu Ala156Glu + Ser154Asp + Gly157Fon + Ser160Glu Ala156Glu + Ser154A								
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Glyl52Glu + Ala15GGly + Ser158Asp + Ser16OGlu Scyl52Asp + Ser158Asp + Ile159Euc + Ser16OGlu Glyl52Asp + Glyl55Gln + Ser158Asp + Ser16OGlu Ala15GGlu + Ser15BGlu + Ile159Euc + Ser16OGlu Ala15GGlu + Ser15BGlu + Ile159His + Ser16OGlu Glyl52Asn + Ser15BGlu + Ile159His + Ser16OGlu Glyl52Asn + Ser154Asp + Glyl57For + Ser16OGlu Asn153Asp + Ser154Asp + Ile159ser + Ser16OGlu Asn153Asp + Ser154Asp + Fer16OAsp + Tyr16IIle Glyl52Asn + Ser154Asp + Ser16OAsp + Tyr16IIle Glyl52Asn + Ser154Asp + Ser16OAsp + Tyr16IIle Glyl52Asn + Ser154Glu + Glyl57Glu + Ser158Asp Glyl52Asn + Ser154Glu + Glyl57Glu + Ser158Asp Asn153Asp + Ser154Glu + Ala156Ser + Glyl57Asp Asn153Glu + Ser154Glu + Glyl55Ser + Glyl57Asp Ser154Glu + Glyl55Asp + Glyl57For - Ser16OAsp								
35 Gly152Asp + Ser158Asp + Ile159Leù + Ser160Glu Gly152Asp + Gly155Gln + Ser158Asp + Ser160Glu Ala156Glu + Ser158Glu + Ser166Asp + Tyr161Gly Gly157Asp + Ser158Glu + Ile159Ris + Ser160Glu Gly152Asn + Ser154Glu + Gly155Asp + Ser160Glu Gly152Asn + Ser154Glu + Gly155Asp + Ser160Glu Asn153Glu + Ser154Asp + Gly157Pro + Ser160Glu Asn153Asp + Ser154Asp + Ile159Ser + Ser160Glu Asn153Asp + Ser154Asp + Ser160Asp + Tyr161Ile Gly152Asn + Ser154Glu + Gly157Glu + Ser158Asp Gly152Glu + Ala156Asp + Ser158Glu + Ile159Val 45 Asn153Asp + Ser154Glu + Ala156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Fro + Ser160Asp								
Alā156Glù + Ser158Glu + Ser16GAsp + Tyr16IGly Gly157Asp + Ser158Glu + Ile159His + Ser160Glu Gly152Asn + Ser154Glu + Gly155Asp + Ser160Glu 40 Asn153Glu + Ser154Asp + Gly157Pro + Ser160Glu Asn153Asp + Ser154Asp + Ile159ser + Ser160Glu Asn153Asp + Ser154Asp + Ile159ser + Ser160Glu Asn153Asp + Ser154Glu + Gly157Glu + Ser158Asp Gly152Glu + Ala156Asp + Ser158Glu + Hel59Val 45 Asn153Asp + Ser154Glu + Ala156ser + Gly157Asp Asn153Glu + Ser154Glu + Ala156ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Err + Ser16GAsp	35	Gly152Asp	÷	Ser158Asp	+	Ile159Leu	+	Serl 60Glu
Alāi56Glù + Seri58Glu + Seri60Asp + Tyri6iGly Gly157Asp + Seri58Glu + Ilei59His + Seri60Glu Gly152Asn + Seri54Glu + Gly155Asp + Seri60Glu Asni53Glu + Seri54Asp + Gly157Pro + Seri60Glu Asni53Asp + Seri54Asp + Ilei59ser + Seri60Glu Asni53Asp + Seri54Asp + Seri60Asp + Tyri6ille Gly152Asn + Seri54Glu + Gly157Glu + Seri58Asp Gly152Glu + Alai56Asp + Seri58Glu + Ilei59Val 45 Asni53Asp + Seri54Glu + Alai56ser + Gly157Asp Asni53Glu + Seri54Glu + Alai56ser + Gly157Asp Seri54Glu + Gly155Asp + Gly157Err + Seri60Asp		Glv152Asp	÷	Gly155Gln	4	Ser158Asp	÷	Ser160Glu
Gly157Asp + Ser158Glu + Ile159His + Ser160Glu Gly152Asn + Ser154Glu + Gly155Asp + Ser158Asp 40 Asn153Glu + Ser154Asp + Gly157Fro + Ser160Glu Asn153Asp + Ser154Asp + Ile159Ser + Ser160Glu Asn153Asp + Ser154Asp + Ser160Asp + Tyr16Ille Gly152Asn + Ser154Asp + Ser160Asp + Tyr16Ille Gly152Glu + Ale156Asp + Ser154Glu + Ser158Asp Gly152Glu + Ale156Asp + Ser158Glu + Ile159Val 45 Asn153Asp + Ser154Glu + Ale156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157For - Ser160Asp		Ala156Glu	-+	Ser158Glu	÷	Ser160Asp	4	Tvr161Glv
Glý152Asn + Ser154Glu + Gly155Asp + Ser158Asp Asn153Glu + Ser154Asp + Gly157Pro + Ser160Glu Asn153Asp + Ser154Asp + Ile159ser + Ser160Glu Asn153Asp + Ser154Asp + Ile159ser + Ser160Glu Asn153Asp + Ser154Glu + Gly157Glu + Ser158Asp Gly152Glu + Ala156Asp + Ser158Glu + Ile159Val 45 Asn153Asp + Ser154Glu + Ala156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Fro + Ser16GAsp								
40 Asn153Glu + Ser154Asp + Gly157Pro + Ser160Glu Asn153Asp + Ser154Asp + Ile159Ser + Ser160Glu Asn153Asp + Ser154Asp + Ser160Asp + Tyr16Ille Gly152Asn + Ser154Glu + Gly157Glu + Ser158Asp Gly152Glu + Ale156Asp + Ser158Glu + Ile159Val 45 Asn153Asp + Ser154Glu + Ale156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Fro + Ser160Asp								
Asn153Asp + Ser154Asp + 1le159ser + Ser160Glu Asn153Asp + Ser154Asp + Ser160Asp + Tyr161Ile Gly152Asn + Ser154Glu + Gly157Glu + Ser158Asp Gly152Glu + Ala156Asp + Ser158Glu + Ile158Val Asn153Asp + Ser154Glu + Ala156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157For + Ser160Asp	40							
Asn153Asp + Ser154Asp + Ser160Asp + Tyr16IIle Gly152Asn + Ser154Glu + Gly157Glu + Ser158Asp Gly152Glu + Ala156Asp + Ser158Glu + Ile158Val 45 Asn153Asp + Ser154Glu + Ala156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Fro + Ser160Asp								
G1y152Asn + Ser154G1U + G1y157G1U + Ser158Asp G1y152G1U + Ala156Asp + Ser158G1U + Ile159Val 45 Asn153Asp + Ser154G1U + Ala156Ser + G1y157Asp Asn153G1U + Ser154G1U + G1y155Ser + G1y157Asp Ser154G1U + G1y155Asp + G1y157Fro + Ser16GAsp								
Glý152Glu + Ala156Asp + Ser158Glu + Ile159Val 45 Asn153Asp + Ser154Glu + Ala156Ser + Gly157Asp Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Fro + Ser160Asp								
45 Ashi53Asp + Ser154Glu + Ala156Ser + Gly157Asp Ashi53Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Fro + Ser16GAsp								
Asn153Glu + Ser154Glu + Gly155Ser + Gly157Asp Ser154Glu + Gly155Asp + Gly157Pro + Ser160Asp	45							
Ser154Glu + Gly155Asp + Gly157Prc + Ser160Asp								
		Ser15461:	4.	G1v1558en	4	Glw157Pro	4	Sarianan
Salarah . Wattootto . Octionsto . Ilciobate								
								~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~

TABLE 19

Loop 5 - Single Mutation Variants
Ala181Asn

WO 95/30011 PCT/US95/04760

	Ala181Asp	
	Ala181Gln	
	Alal81Glu	
	Ala181Glv	
5	Ala181His	
	Ala181Pro	
	Ala181Ser	
	Ala181Thr	
	Ser182Asp	
10	Ser182Glu	
	Phe183Ala	
	Phe183Asn	
	Phe183Asp	
	Phel83Cys	
15	Phe183Gln	
	Phel83Glu	
	Phe183Gly	
	Phel83His	
	Phel831le	
20	Phe183Leu	
	Phel83Met	
	Phe183Pro	
	Phel83Ser	
	Phel83Thr	
25	Phe183Tyr	
	Phe183Val	
	Ser184Asp	
	Ser184Glu	
	Gln185Asn	
30	Gln185Asp	
	Gln185Glu	
	Gln185Ser	
	m' m m m m	
	TABLE 20	
35	Loop 5 - Double Mutation Variants	
	Alal81Asp + Phel83Gln	
	Ser182Asp + Gln185Asn	
	Phel83Met + Gln185Glu	

35	Loop 5 - Double Mutation Variants
	Ala181Asp + Phe183Gln
	Ser182Asp + Gln185Asn
	Phe183Met + Gln185Glu
	Ser182Glu + Gln185Asn
40	Ala181Pro + Serl82Glu
	Alal81Asn + Gln185Glu
	Ser182Glu + Phe183Leu
	Ala181Pro + Gln185Asp
	Phe183Ser + Gln185Glu
45	Ala181Gln + Ser182Glu
	Phe183Ile + Gln185Glu
	Alal81Ser + Gln185Asp
	Alal81Gln + Phel83Ser
	AlalBiThr + Phel83Asn
50	Ala181Gly + Gln185Asp
	Ala181His + Serl82Glu
	Phe183Gln + Gln185Ser

	41	
	Phe183Pro + Gln185Ser	
	Ala181Asn + Ser182Asp	
	Alal81Ser + Gln185Glu	
	Ala181Asn + Phe183Asn	
	Ala181His + Phel83Asp	
	Ala181Asn + Serl82Glu	
	Ser182Asp + Phe183His	
	Ala181Asp + Phel83Ile	
	Phe183Leu + Gln185Asp	
)	Ser182Glu + Phe183Ser	
	AlaiSiHis + Gln185Asp	
	Phe183Val + Gln185Asp	
	Ser182Asp + Phe183Thr	
	Phe183Gly + Gln185Asp	
i	Alai8iThr + Gln185Glu	
	Ala181His + Gln185Glu	
	Ser182Asp + Phe183Val	
	Alal81Asp + Phel83Ser	
	Ser182Asp + Phe183Cys	
)	Ala181Pro + Phe183Asp	
	Ala181Gly + Phe183Ala	
	Ala181Pro + Phe183Asn	
	Phel83Pro + Gln185Asp	
	Ser182Glu + Phe183Tyr	
5	Phe183Cys + Gln185Ser	
	Alal81Thr + Ser182Glu	
	Ala181Pro + Phe183Ala	
	Ser182Glu + Phe183Thr	
	Ala181Pro + Phe183Pro	
0	Ser182Glu + Gln185Ser	
	Ala181Gln + Ser182Asp	
	Phe183Gly + Gln185Glu	
	Ala181Gln + Gln185Asp	
	Phe183Ser + Gln185Asp	
5	Serl#2Asp + Phel#3Met	
	Phe183Ala + Gln185Asn	
	Ala181Asp + Phe183His	
	Phel83Val + Glnl85Glu	
	Ala181Ser + Ser182Glu	
0	Alal81Asn + Phel83Pro	
	Phe183Tyr + Gln185Glu	
	Ala181Glo + Phe183Cys	
	Ser182Glu + Phe183Ile	

45 TABLE 21

Loop 5 - Triple Mutation Variants

Ala181G1u + Phe183Va1 + GIn185Ser
Ala181Pro + Ser1825sp + GIn185Asn

Ala181Pro + Ser182Asp + Gln185Asp Ala181Thr + Phel83His + Gln185Asp 50 Ser182Glu + Phel83Ala + Gln185Asp Ala181Thr + Ser182Asp + Gin185Asn Ala181Gln + Ser182Asp + Phel83Ala

			42			
			Phel83Asn			
	Ala181Gln					
			Phel83Met			
	Alal8lPro					
5	Alal81His					
	Alal81Ser					
	Ala181Gly					
	Ala181Asn					
	Ser182Asp	4	Phel83Leu	4.	Gln185Asn	
10			Phel83Val			
	Ala181Glu					
			Phe183Tyr			
			Ser182Asp			
	Ala181Thr	÷	Phel83Ile	÷	Gln185Ser	
15	Ala181Gln	+	Ser182Glu	÷	Gln1855er	
	Alal81Gln					
	Ala181Asp	÷	Phel83Ala	+	Gln185Asn	
			Ser182Asp			
	Ala181Ser	+	Phe183Pro	÷	Gln185Glu	
20	Ser182Glu	÷	Phel83Ala	4	Gln185Ser	
	Ala181Asn	÷	Phe183Cys	+	Gln185Ser	
	Ala181Pro	÷	Phel83Thr	+	Gln185Asp	
	Alal81Thr	+	Phe183Val	÷	Gln185Asn	
	Ala181Gln	÷	Ser182Asp	+	Gln185Ser	
25	Ala181Asn	+	Ser182Asp	+	Gln185Ser	
	Ser182Asp	+	Phel83Thr	4	Gln185Ser	
	Ala181Ser	÷	Phe183Asp	+	Gln185Asn	
			Phel83Thr			
	Ala181Gly	ź	Phe183Asn	+	Gln185Ser	
30			Phel83Met			
	Ala181Asp	4	Phe183Pro	+	Gln185Asn	
			Ser182Asp			
	Ala181Gln	+	Ser182Glu	÷	Gln185Asn	
	Ala181Thr	+	Ser182Asp	+	Gln185Ser	
35			Phel83Asn			
	Alal81Thr	÷	Phel83Asp	+	Gln185Ser	
	Ala181Gln	÷	Phe183Ser	÷	Gln185Ser	
	Ser182Asp	4.	Phe183Gly	*	Gln185Ser	
	Ala181Gly	+	Ser182Glu	+	Phel83Leu	
40			Ser182Glu			
	Ala181Glu	÷	Ser182Glu	÷	Phel83Ser	
			Ser182Glu			
			Ser182Glu			
	Ala181Glu	4	Ser182Glu	+	Phe183Val	
45	Ala181Glu	÷	Ser182Asp	+	Phe183Met	
			Ser182Asp			
	Alal81Asp	+	Ser182Asp	÷	Phel83Cys	
	Ala181Glu	+	Ser182Asp	-9-	Gln185Asn	
			Ser182Asp			
50			Ser182Glu			
•	Ala181Asp	÷	Ser182Glu	÷	Phel83Ser	
			Ser182Asp			
	Alal81Glu	4	Ser182G10	÷	Phel83Thr	
	Ala1816lu	+	Ser182Asp	+	Phel83Leu	

TABLE 22

	TABLE 22							
			p 5 - Quadrup					
			Ser182Asp					
5			Serl82Glu					
	Ala181Gly	÷	Ser182Asp	4	Phe183Gly	÷	Gln185Asn	
	Ala181Gly	÷	Serl82Glu	4	Phel83Pro	+	Gln185Ser	
	Ala181Thr	+	Ser182Glu	÷	Phe183Thr	÷	Gln185Ser	
	Ala181Gly	÷	Ser182Glu	+	Phe183Thr	÷	Gln185Ser	
10	Ala181His	+	Serl82Glu	÷	Phe183His	+	Gln185Asn	
	Ala181Gly	+	Serl82Glu	+	Phel83Ser	4	Gln185Ser	
	Ala181Gln	÷	Ser182Glu	+	Phel83His	4	Gln185Asn	
	Ala181Asn	÷	Ser182Glu	÷	Phe183Cys	+	Gln185Ser	
	Ala181Pro	÷	Serl82Glu	+	Phe183Met	÷	Gln185Ser	
15	Ala181Gln	÷	Ser182Asp	÷	Phe183Gln	4	Gln185Asn	
	Ala181Thr	+	Ser182Asp	+	Phel83His	4	Gln185Asn	
	Ala181Gly	÷	Ser182Glu	+	Phel83Leu	4	Gln185Ser	
	Ala181Asn	÷	Ser182Asp	+	Phel831le	÷	Gln185Ser	
	Ala181Gly	÷	Ser182Asp	4	Phe183Ala	4	Gln185Ser	
20	Ala181Asn	+	Ser182Asp	÷	Phe183Ser	*	Gln185Asn	
	Ala181Asn	+	Ser182Glu	+	Phel83Gly	4	Gln185Ser	
	Alal@lAsn	4	Ser182Glu	+	Phel83Met	4	Gin185Asn	
	Ala181His	+	Ser182Glu	+	Phe183Asn	÷	Gln185Asn	
	Alal81Gly	+	Ser182Glu	4	Phel83Tyr	4	Gln185Asn	
25	Ala181Asn	÷	Ser182Asp	÷	Phe183Asn	÷	Gln185Asn	
	Ala181Glu	+	Ser182Glu	+	Phe183Asn	4	Gln185Asn	
	Ala181Asp	÷	Ser182Glu	+	Phe183Ile	÷	Gln185Asn	
	Alal81Glu	4	Ser182Asp	4	Phe183Gln	+	Gln185Asn	
	Ala181Asp	+	Ser182Asp	÷	Phe183His	+	Gln185Asn	
30	Ala181Glu	+	Ser182Asp	+	Phe183Ser	÷	Gln185Asn	
	Ala181Glu	4	Ser182Asp	÷	Phe183Leu	÷	Gln185Asn	
	Ala181Glu	4	Ser182Asp	4-	Phe183Leu	+	Gln185Ser	
	Ala181Asp	÷	Ser182Glu	4	Phel83Thr	+	Gln185Ser	
	Ala181Asp	+	Ser182Asp	+	Phe183Gln	+	Gln185Asn	
35	Ala181Asp	÷	Serl82Asp	+	Phe183Ala	4	Gln185Ash	
	Ala181Asp	4	Ser182Glu	+	Phel83Ala	4	Gln185Asn	
	Alal81Glu	+	Ser182Asp	4	Phe183Met	+	Gln185Ser	
			Ser102Glu					
			Ser182Asp					
40			Ser182Asp					
			Serl82Glu					
			Ser182Asp					
			Ser182Asp					
			Serl82Glu					
45			Ser182Asp					
			Ser182Asp					
			Ser182Asp					
			Ser182Glu					
			Ser182Glu					
50			Ser182Asp					
			Ser182Asp					
	Ala181Pro	÷	Ser182Asp	+	Phel83Glu	÷	Gln185Asp	

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	Ala181Asn	+	Ser182Glu	4	Phel@3Asp	-3-	Gln185Asp
	Ala181Thr	+	Ser182Asp	÷	Phel83Asp	4	Gln185Glu
	Alal81Pro	4	Ser182Glu	÷	Phel83Glu	÷	Gln185Glu
	Ala181Asn	4	Ser182Asp	÷	Phe183Asp	4	Gln185Glu
5	Alal@IThr	4	Ser182Glu	+	Phe183Asp	4	Gln185Asp
	Alal81His	4	Ser182Glu	÷	Phe183Glu	+	Gln185Glu
	Alal81Glu	4	Ser182Glu	4	Phel83Ser	4	Gln185Glu
	Ala181Glu	4	Ser182Glu	÷	Phe183Val	÷	Gln185Glu
	Ala181Asp	÷	Ser182Glu	+	Phel83Pro	÷	Gln185Glu
10	Ala181Glu	÷	Ser182Glu	+	Phe183Thr	+	Gln185Asp
	Alal81Asp	+	Ser182Asp	+	Phel83Cys	+	Gln185Glu

	TABLE 23
	Loop 6 - Single Mutation Variants
15	Val193Ala
	Val193Asn
	Vall93Asp
	Val193Cys
	Val193Gln
20	Vall93Glu
	Vall93Gly
	Val193His
	Val193Met
	Vall93Pro
25	Val193Ser
	Vall93Thr
	Ala194Asn
	Ala194Asp
	Ala194Gln
30	Ala194Glu
	Ala194Gly
	Ala194His
	Ala194Pro
	Ala194Ser
35	Ala194Thr
	Pro195Asn
	Pro195Asp
	Pro195Gln
	Prol95Glu
40	Pro195Gly
	Pro195Ser
	Gly196Asn
	Gly196Asp
	Gly196Gln
45	Gly196Glu
	Gly196Pro
	Gly196Ser
	Val197Ala
	Val197Asp
50	Vall97Cys
	Vall97Gln
	Vall97Glu

	Vall97Gly
	Val197His
	Val197Met
	Val197Pro
5	Vall97Ser
	Val199Ala
	Vall99Asn
	Val199Asp
	Vall99Cys
10	Vall99Gln
-	Vall99Glu
	Val199Gly
	Val199His
	Vall99Met
15	Val199Pro
***	Vall99Ser
	Vall99Thr
	Gln200Asn
	Gln200Ser
20	Ser201Asp
20	Ser201G1u
	Thr202Asn
	Thr202Asp
	Thr202Gln
25	Thr202Glu
23	Thr202Gly
	Thr202Pro
	Thr2025er
	Tyr203Ala
30	Tyr203Asn
30	Tyr203Asp
	Tvr203Gln
	Tvr203His
	Tyr20311e
35	Tyr203Met
33	Tyr203Pro
	Tvr203Ser
	Pro204Asn
	Pro204Asp
40	Pro204Gln
40	Pro204Glu
	Pro204Gly
	Pro204Ser
	G1y205Asn
45	G1y205Asp
40	G1y205G1n
	G1y205G1u
	G1v205Pro
	Gly205Ser
50	Ser206Asp
au au	Ser206Glu
	Thr207Asn
	Thr207Gln
	Thr207Glu
	111207610

	46	
	Thr207Glv	
	Thr207Pro	
	Thr207Ser	
	Tyr208Ala	
5	Tyr208Asn	
	Tyr208Asp	
	Tyr208Cys	
	Tyr208Gln	
	Tyr208Glu	
10	Tyr208Gly	
	Tyr208His	
	Tyr20811e	
	Tyr208Leu	
	Tyr208Met	
15	Tyr208Pro	
	Tyr208Val	
	Ala209Asn	
	Ala209Asp	
	Ala209Gln	
20	Ala209Glu	
	Ala209Gly	
	Ala209His	
	Ala209Pro	
	Ala209Ser	
25	Ala209Thr	
	Ser210Asp	
	Ser210Glu	
	Leu211Ala	
	Leu211Asn	
30	Leu211Asp	
	Leu211Cys	
	Leu211Gln	
	Leu211Gly	
35	LeuZllHis - LeuZllIle	
23	Leu211Met	
	Leu211Pro	
	Leu211Ser	
	Leu211Thr	
40	Leu211Val	
40	Asn212Glu	
	Gly213Asn	
	Gly213Asp	
	Gly213Gln	
45	G1y213Glu	
	Gly213Pro	
	Gly213Ser	
	Thr214Asn	
	Thr214Asp	
50	Thr214Gln	
	Thr214Glu	
	Thr214Gly	
	Thr214Pro	
	Thr214Ser	

TABLE 24

	TABLE 24	
	Loop 6 - Double Mutation Variants	
	Gly196Asn + Ala209Asp	
5	Vall99Ser + Tyr208Asn	
	Pro195Asn + Thr207Asp	
	Vall97Ala + Asn2l2Asp	
	Asn198Gln + Thr2075er	
	Vall99Gly + Tyr208Ile	
10	Gly196Asn + Ala209Pro	
	Val199Gly + Gln200Ser	
	Pro195Ser + Gly205Gln	
	Val199Ser + Leu2l1Asp	
	Gly196Gln + Val197Asn	
15	Thr202Asn + Thr214Glu	
	Ala194Thr + Thr202Pro	
	Val199Asn + Ser210Glu	
	Thr202Ser + Asn212Gln	
	Ser210Asp + Thr214Asn	
20	Pro195Gly + Asn212Asp	
	Asn198Gln + Tyr208Gln	
	Val197Asn + Thr214Glu	
	Tyr208Asp + Leu211Gln	
	Thr202Ser + Ser210Glu	
25	Val197Cys + Ser210Glu	
	Gln200Glu + Tyr203Gly	
	Ala209Thr + Leu211Glu	
	Val197Ser + Gln200Glu	
	Thr202Gly + Ser210Glu	
30	Gln200Ser + Gly213Pro	
	Gly196Ser + Thr207Gly	
	Pro204Gln + Ser210Glu	
	Val199Cvs + Pro204Gly	
	Gly213Pro + Thr214Pro	
35	Gly196Asn + Ser210Glu	
**	Thr207Gln + Ser210Glu	
	Vall99Met + Gln200Asp	
	Thr202Ser + Tvr203Ile	
	Pro195Ser + Asn212Ser	
40	Vall97Glu + Tvr208Gln	
	Asn198Glu + Leu2l1Cys	
	Gly196Gln + Ser206Glu	
	Ala194Ser + ThrZl4Ser	
	Val197Ser + Tvr203Ala	
45	Ser210Asp + Gly2l3Pro	
**	Tyr203His + Gly213Asp	
	Val197Ser + Val199Ser	
	Ala209Pro + Ser210Asp	
	Thr207Asp + Thr214Ser	
50	Thr207Gly + Ala209His	
•	Pro195Asn + Asn198Asp	
	Val197Pro + Ser206Asp	
	*	

	Gln200Ser	*	Asn212Asp
	Vall97Thr	t	Asn212Asp
	Gln200Asn	÷	Thr214Glu
	Ala209Asp	+	Thr214Ser
5	Ala209Asn	4	Asn212Ser
	Ala194Ser	4	Asn212Glu
	Val197Glu	4	Gly213Asn
	Tyr203Cys	+	Asn212Asp
	Pro195Gln	÷	Val197Cys
10	Asn198Ser	÷	Tyr208Ala
	Gly205Gln	÷	Ala209Glu
	Gly205Ser		Leu211Ser
	Gly205Gln	÷	Tyr208Ala
	Ala194Ser	+	Asn198Asp
15	Ala194Thr	4	Pro1955er
	Val199Thr	4	Pro204Glu
	Thr202Glh	+	Ser210Asp
	Ser206Glu	+	Leu211His
	Asn198Glu	4	Thr202Asn
20	Ser210Asp	+	Gly213Ser
	Gly196Ser	+	Thr202Gln
	Pro204Gln	+	Gly213Asp
	Asn198Glu	+	Pro204Gly
	Thr202Gly	*	Tyr208Met
25	Pro195Gly	÷	Gly213Glu
	Pro195Ser	+	Pro204Asp
	Pro195Ser	÷	Tyr203Thr
	Alal94Asn	4-	Tyr203Pro
	Ala194Pro	+	Gln200Asp
30	Pro204Asp	÷	Gly205Asn
	Gly196Pro	+	Asn198Gln
	Thr207Ser	÷	Leu211Gly
	Pro195Ser	+	Leu211Ile
	Pro204Glu	+	Leu211Gly
35	Vall99Ser	÷	Tyr208Ala
	Gly196Ser	+	Ser210Asp
	Ala194Thr	+	Leu211Gly
	Thr207Ser	÷	Ser210Glu
	Gly196Pro	÷	Thr207Glu
40	Pro204Glu	÷	Leu211Met
	Prol95Asn	÷	Asn198Ser
	Tyr203Met	+	Thr207Gln
	Pro204Gly	+	Ala209Glu
	Val197Glu	÷	Asn212Ser
45	Pro1955er	÷	Ala209Pro
	Gly196Ser	÷	Leu211Gly
	Gly205Pro	+	Leu211Met
	Vall97Gln	+	Pro204Ser
	Vall99Asn	+	Ser206Asp
50	Val197Asp	+	Thr202Asn
	Gly196Gln	+	Thr214Gly
	Pro204Asn	+	Asn212Gln
	Vall99Asn	÷	Gln200Asn
	Pro195Gly	+	Leu211Gly

	mu=2620us	+	Pro204Ser
	Tyr203Cys Gln200Asp		Leu211Cvs
		* *	Ser210Glu
	Asn198Gln		
	Alal94Gly	÷	Gln200Glu
5	Gly196Gln	÷	Pro204Glu
	Vall97Pro	÷	Thr202Asn
	Ala194Gly	÷	Vall99Ala
	Ala194Thr	÷	Leu2llAsn
	Asn198Gln	÷	Gly205Asp
10	Tyr203Asn	÷	Leu211His
	Asn212Asp	÷	Gly213Gln
	Asn198Gln	÷	Ser206Asp
	Vall99Thr	÷	Gln200Glu
	Thr202Ser	4	Asn212Asp
15	Ala194Gly	÷	Ser210Glu
	Ser206Glu	4	Ala209Asn
	Ala209Asp	+	Asn212Ser
	Val199Gly	÷	Asn212Ser
	Ala194Pro	+	Gly213Asp
20	Gln200Asp	÷	Pro204Gly
20	Vall97Thr	+	Tyr203Ala
	Asn198Gln	+	Leu211Pro
	Pro195Gln	+	Leu211Gln
		4	Thr214Glu
**	Gly196Gln		
25	Pro195Asn	+	Ser210Glu
	Thr207Asn	+	Leu211Asp
	Ser210Glu	÷	Gly213Pro
	Gly205Pro	+	Thr207Asp
	Gln200Glu	*	Thr202Gln
30	Thr202Ser	+	Gly213Asp
	Pro204Gln	÷	Thr214Gln
	Gly196Ser	+	Gln200Asp
	Val197Ser	*	Gln200Asp
	Thr202Pro	÷	Thr207Asp
35	Tyr203Thr	Ť	Tyr208His
	Pro195Gln	÷	Thr202Asn
	Vall97Asn	4	Asn212Asp
	Vall97Met	4	Thr202Gln
	Vall99Met	÷	Thr202Pro
40	Ala209Glu	t	Leu211Met
	Gly196Asn	÷	Val199His
	Ala194Gly	+	Ser206Glu
	Gly196Asn	÷	Pro204Asn
	Gly196Asn	ተ	G1n200G1u
45	Vall97Ser	÷	Ser210Asp
	Pro195Gln	÷	Pro204Gln
	Ala194His	4	Asnl98Gln
	Val197Cys	÷	Asn212Gln
	Asn198Glu	÷	Ala209Ser
50	Ala194Gln	÷	Vall99Pro
***	Asn198Asp	÷	Vall99Gln
	Asn198Asp	÷	
	Pro204Asn	+	
	Tyr203Ser		
		+	Tyr208Leu

	Gly196Gln	4	Ala209Asp
	Ser206Glu	4	Asn212Gln
	Thr207Ser	4	Ala209His
	Vall97Thr	+	Ser230Asp
5	Tyr208Gln	4	Ser210Asp
	Asn198Ser	.ş.	Ser210Glu
	Glv196Ser	÷	Thr214Asp
	Ala194Gin	÷	Thr202Asn
	Pro195Gly	+	Thr214Asn
10	Leu211Thr	÷	Thr214Asp
	Pro195Ser	÷	Asn198Glu
	Gly196Ser	÷	Gly205Ser
	Alal94His		
	Thr207Gly	+	Tyr208Met
15	Ala1945er	÷	Val197His

	Loop 6 - Tripl		
	Alal94Thr + Se	r206Glu +	Tyr208Cys
20	Gly196Asn + Ty:	:203Pro +	Ala209Gly
	Pro195Gly + Asi	n1985er +	Thr207Glu
	Pro195Gly + Gl		
	Tyr203Leu + Pro	204Gln +	Gly205Gln
	Gly196Gln + Va		
2.5	Leu211Ser + Gl	y2135er +	Thr214Gln
	Pro195Asn + Pro	204Glu +	Gly205Gln
	Asn198Asp + Th:	202Gly +	Gly213Gln
	Tyr203Ala + Let	1211His +	Thr214Gln
	Ala194Thr + Va		
30	Alai94Gln + Th		
	Gly196Asn + Pro	204Gln +	Ala209Asn
	Thr202Pro + Ty:	r208Asp +	Leu211Thr
	Vall97Gly + Ala		
	Gly196Ser + Gl		
35	Ala194Ser + Va.		
	Glyl96Asn + Ası		
	Alal94Thr + Ala		
	Ala194Pro + Pro		
	Thr202Ser + Ty		
40	Thr202Ser + Ty		
	Ala194Ser + Pro		
	Alai94Pro + Thi		
	Gly196Asn + Se		
	Gly196Ser + Gly		
45	Alal94Thr + Val		
	Pro204Glu + Ala		
	Gly196Ser + Gly		
	Val197Cys + Thi		
	Asn198Ser + Pro		
50	Alal94Gly + Ala		
	Glyl96Pro + Ty		
	Vall99Ala + Th	207Asn +	Tyr208Val

	Tyr203Cys	+	Ser210Asp	÷	Leu211Pro
	Ala194Ser	+	Vall97Ser	4	Gln200Asp
	Ala194Asn	4	Pro195Gly	÷	Leu21111e
	Vall99Ser	+	Leu2l1Asn	+	Gly213Asp
5	Ala194Asn	+	Ser206Glu	4	Thr214Gly
	Ala194Gly	+	Pro195Gly	+	Val197Asp
	Pro195Gln	+	Ala209Ser	4	Ser210Asp
	Val197Thr	+	Asn198Gln	+	Tyr203Leu
	Vall97Ala	4	Thr202Gln	+	Ser206Glu
10	Gly196Pro	+	Pro204Glv	+	Asn212Glu
10	Thr202Gly	4	Pro204Glu	+	Tyr208Ser
	Gln200Ser	+	Thr202Pro	+	Pro204Ser
	Gin200Glu	4	Tyr203Thr	ų.	Pro204Asn
	Asn198Asp	+	Vall99Gln	į.	Pro204Asn
15	Ala194Pro	4	Pro195Gln	÷	Vall99Gly
13	Pro195Asn	+	Pro204Asn	4	Ser206Glu
	Thr202Ash	+	Leu211Thr	4	Asn212Gln
	Gly196Gln	4	Thr202Pro	4	Gly213Asp
	Asn198Glu	+	Gln200Asn	+	Leu211Gly
20	Val199Gly	+	Thr202Gln	4	G1y213G1u
20	Tyr203Ser	+	Thr207Pro	4	Ser210Asp
		4		+	
	Pro195Gly Pro195Gly	+	Gly196Gln Thr207Glv	+	Vall97Glu Tvr208Ser
	Thr202Gly	+	Leu211Glu	+	Gly213Gln
25		+		+	
25	Val197Gly	+	Thr202Pro G1v205Gln	+	Asn212Glu Ser206Glu
	Gly196Gln	4	Val199Thr	+	Thr214Glu
	Pro195Gly	4	Gln200Ser	+	Leu211Asp
	Gly196Ser Gly196Asn	4	Tvr208Glu	4	Thr214Pro
30	Tyr203Thr	4	Pro204Asn	+	Ser206Glu
30	Vall99Thr	+	Thr202Asn	+	Tyr208Gly
	Thr202Pro	+	Tyr203Thr	+	Pro204Glu
	Glv196Gln	÷	Asn212Asp	+	Thr214Gln
	Pro195Gly	4	Thr202Gly	+	Asn212Ser
35	Pro195Gly	ż	Tyr208Gln	4	Ser210Asp
23	Ala194Pro	+	Ser206Glu	+	Leu2115er
	Alal94His	+	Pro204Asn	+	Gly213Gln
	Gly196Ser	7	Tyr208Met	+	Ser210Asp
	Vall97Glu	4	Val199Ser	4	Tyr203Asn
40	Thr202Gly	4	Ala209Asn	4	Asn212Asp
40	Val197Ser	+	Ser210Asp	+	Glv213Pro
	Ala194Ser	4	Tyr208Ile	4	Asn212Glu
	Ala194Gly	4	Asn198Gln	+	Ala209His
	Alai94Ser	4	Thr207Pro	4	Glv213Glu
45	Vall99Thr	4	Leu211Asp	*	Asn212Ser
43	Vall99Pro	4	Thr202Ser	+	Leu211Asn
	Ser206Glu	÷	Tyr208Cys	+	Thr214Asn
	Ala2095er	†	Leu211Ile	+	Asn212Glu
	Asn198Glu	+	Tyr208Ala	+	Ala209Ser
60	Alal94Pro	+		+	
50	Alai94Asn	+	Pro195Ser	4	Leu211Glu
	Gly196Pro	+	Pro204Gly	4	Glv205Pro
	Tyr2031le	+	Tyr208Thr	4	Ala209Glu
	Gly196Gln	+	Thr202Gln	4	Asn212Asp
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	Ala194Asn	4	Val197Pro	÷	Thr202Pro
	Ala194Gln	+	Val199Gly	4	Ala209Asp
	Ala194Ser	÷	Pro195Gly	4	Asn212Gln
	Pro195Gln	÷	Tyr203Pro	÷	Ser210Asp
5	Vall97Thr		Thr202Gln	+	Tyr208Asn
,	Alal94Thr	+	Gly196Ser	+	Leu211Asn
	Ala194Gly	+	Thr202Ser	4	Pro204Asp
	Ala194Gly		Gly205Glu	4	Gly213Ser
	Vall99Pro	4	Thr207Pro	4	Tyr208Met
10	Ala194Pro	4	Asn198Glu	4	Ala209His
10	Tyr208Leu	+	Ser210Glu	÷	Thr214Pro
	Gly196Asn	÷	Vall99Ala	+	Gly205Asp
	Gly196Pro	+	Gly205Glu	+	Tyr208Ser
		4		4	Val197Cys
	Pro195Asn		Gly196Gln	4	
15	Asn198Ser	+	Gln200Glu		Leu211Asn Thr214Gln
	Thr202Ser	÷	Tyr203Cys	4	
	Ala194Ser	+		÷	Thr207Asp
	Gly196Ser	+	Gly205Glu	÷	Tyr2081le
	Tyr203Met	+	Gly205Asn	+	Gly213Pro
20	Pro204Gln	+		+	Ala209His
	Gly205Asn	÷	Leu211Asp	4	Thr214Ser
	Tyr203Met	+	Ala209His	+	Leu211Met
	Vall99Asn	÷	Thr202Ser	+	Gly213Glu
	Vall97Thr	+	Pro204Asp	÷	Asn212Gln
25	Ala194Gly	÷	Ser210Glu	4	Leu211Pro
	Vall97His	4	Ala209Gly	÷	Ser210Asp
	Gln200Glu	÷	Thr202Gln	÷	Tyr208His
	Ala194Ser	4	Ser206Asp	+	Leu211Ala
	Pro195Ser	ş	Asn198Asp	4	Gly205Pro
30	Tyr203Pro	4	Thr207Asp	4	Thr214Pro
	Pro195Ser	+	Val199His	4	Leu211Pro
	Tyr203Met	ŧ	Thr207Glu	+	Ala209His
	Vall97Cys	÷	Gln200Asn	+	Ser206Glu
	Val197Glu	÷		÷	Tyr208His
35	Pro195Gln	÷	Vall97Cys	÷	Pro204Gly
	Vall99Pro	+	Gly205Ser	÷	Gly213Asp
	Ala194Thr	÷	Thr207Ser	4.	Ala209Glu
	Vall97Met	+	Gly205Pro	4	Tyr208Gly
	Gly196Ser	÷	Gly205Glu	4	Ala209Thr
40	Pro195Ser	+	Vall99Thr	÷	Gly205Ser
	Ala194Ser	4	Asn198Asp	4	Gly213Ser
	Asn198Glu	+	Vall99Ser	÷	Thr207Pro
	Ala194Thr	+	Gly196Pro	+	Ser2l0Glu
	Gly196Asn	÷	Thr202Pro	٠	Leu211Met
45	Tyr203Met	4	Asn212Asp	ተ	Thr214Ser
	Tyr203Gly	4	Ala209Ser	÷	Ser210Asp
	Ala194Ser	4	Thr207Ser	÷	Leu211Pro
	Tyr208Cys	4	Gly213Asn	÷	Thr214Pro
	Val197Met	4	Pro204Glu	4	Gly213Ser
SO	Gln200Ser	4	Tyr203Ala	÷	
	Pro195Gly	+	Ser206Asp	+	Leu21111e
	Tyr203Gly	4	Tyr208Asp	+	Leu211Asn
	Vall97Thr	÷	Ser20661u	4	Thr214Pro
	Tvr203Ala	+	Pro204Asn	÷	
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			20			
			* 2 . * 0 * 0 *		2 22 3 22 3	
					Leu211Gln	
					Asn212Glu	
					Pro204Asn	
_			Leu2llSer			
5	Gly196Se					
					Tyr208Cys	
			Leu211Thr			
	Pro195Ası	n +	Vall97Asn	÷	Thr202Pro	
	Vall99Pro Pro195Gl	0 +	Pro204Gly	÷	Gly205Asn	
10	Pro195Gl;	y +	Asn198Asp	÷	Thr214Gly	
					Asn212Gln	
	Pro195Gl:					
					Gly213Glu	
	Pro195Gl	y +	Thr202Pro	÷	Gly205Glu	
15	Thr202Gli	n +	Tyr203Gly	+	Ala209Asn	
	Pro195Ası	h +	Gly196Gln	÷	Asn212Asp	
	Thr202G1;	y +	Tyr208Ile	÷	Leu211Val	
	Asn198Gli	u +	Tyr203Cys	÷	Pro204Gly	
	Ala194Se	4 7	Thr207Ser	4	Ser210Asp	
20	Gln200As	p +	Thr262Pro	4	Tyr203Ala	
	Vall99Cy	3 +	Ala209Gln	÷	Ser210Asp	
	Ala194Ası	n +	Val199Cys	4	Leu211Pro	
	Gln200Se:	r +	Ser210Glu	÷	Leu211Asn	
	Tyr203Gl:	n +	Thr207Glu	÷	Tyr208Ser	
25	Ala194Th	r +	Thr202Asn	4	Thr207Gly	
	Prol95Gl	y +	Glyl96Gln	÷	Ser210Asp	
					Ser206Glu	
	Ala194Ası	n +	Gly196Gln	+	Asn198Glu	
	Vall97Th:	r +	Pro204Gln	*	Gly205Glu	
30	Val199A1:	a +	Gln200Asp	+	Glv213Asn	
	Val197Me	t ÷	Tyr203Val	÷	Gly213Pro	
	Ala194Gl	n +	Tyr203Val	4.	Thr214Glu	
	Val199Cv	s +	Ala209His	+	Leu21lMet	
	かにしてのなべき		Wirw 2027 La	.3.	81.5000016	
35	Ala194Gl	y +	Ser206Glu	÷	Leu2l1Gly	
	Glv196Pr	0 +	Tyr208G1y	4	Ser210Glu	
					Gly205Asp	
			Gly205Asp			

Loop 6 - Quadruple Mutation Variants Pro195Asn + Val197la + Thr207Ser + Asn212Asp Asn198Gln + Val199Gly + Thr207Ser + Asn212Asp Tyr203Ris + Leu211Pro + Asn212Gln + Gly213Gln 45 Ala194His + Asn198Ser + Thr202Asn + Ala209Asp Gly196Gln + Asn198Ser + Thr202Ser + Pro204Glu Pro195Gln + Asn198Gln + Gly205Glu + Ala209Pro Val199His + Pro204Asp + Gly205Glu + Ala209Pro Gly196Gln + Gly205Asn + Ser206Asp + Thr214Ser Gln200Glu + Thr202Pro + Leu211Asn + Gly215Asn Gly196Gln + Pro204Asn + Asn212Gln + Thr214Gly

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TABLE 26

Pro195Gly + Val199Asn + Gln200Asn + Leu211Gly

	Pro195Gln	÷	Pro204Ser	÷	Gly205Glu	4	Tyr2091le
	Vall99Ala	÷	Tyr203Gln	÷	Thr207Gly	+	Ser210Glu
	Ala194His		Vall99Ser	+	Pro204Asn	4	Gly205Glu
	Gly196Pro	+		4	Gln200Asn	4	Ala209Pro
5	Pro195Gln	4	Gln200Asp		Tyr203Asn	÷	Leu211Cys
~	Pro195Ser	+	Thr202Pro	÷	Asn212Asp	+	Thr214Ser
	Ala194Gly	+	Vall97Glu	4	Tyr203Leu	4	Leu211Cys
	Asn198Gln	4	Thr202Pro	4	Tyr208Met	-3-	Thr214Glu
	Gly196Ser	+	Vall99Ser	+	Gly205Gln	4	Ser210Glu
10	Tyr203Ala	+		į	Ser206Asp	4	Leu211Gln
***	Gly196Ser	4	Vall99His	÷	Gln200Asp	+	Thr207Ser
	Pro195Gln	4		÷	Gln200Glu	+	Tyr203Ser
	Gly196Ser	4		+	Gly205Gln	+	Gly213Asn
	Pro195Ser	+	Gly196Asn		Ser206Glu	÷	Thr214Gly
15	Gly196Asn	+	Vall99Asn	+	Ser206Glu	+	Tyr208Pro
8.3	Vall97Gln	+	Gly205Ser	4	Ser210Glu	+	Thr214Ser
	Pro195Asn	+	Gln200Glu		Glv205Asn		Leu211Pro
	Tyr203Pro	÷	Tyr208Kis	1		*	
					Leu211Val	+	Thr214Pro
20	Alal94His	+	Vall99Ser	*	Thr202Gly	+	Tyr208Asp
20	Pro195Asn	+	Vall99Asn	4	Ser206Asp	+	Gly213Ser
	Ala194Ser		Pro195Asn		Vall99Ala	+	Gly205Glu
	Ala194Thr	+		+	Val199Gly	+	Tyr2031le
	Val199Ala	+	Ala209Asp		Leu211Val	+	Asn212Gln
25		+		*		+	Ser210Asp
23	Gln200Ser	+	Thr207Gly		Tyr208Thr	+	Ser210Asp
	Pro204Gly	+	Gly205Asp		Thr207Asn	+	Tyr208Leu
	Ala194Gln	+	Thr202Ser	+	Ala209Ser	+	Asn212Glu
	Vall97Met	+	Thr202Gly			+	Thr214Glu
20	Val199Ala	+	Pro204Gln		Gly205Asp		Tyr208Gly
30	Asn198Glu Gln200Ser	+	Tyr208Cys	+		+	Leu211Val
		+	Pro204Ser Vall97Thr	*		+	LeuZllGlu
	Pro195Ser Pro195Asn	4	Thr202Asn	+	Gly205Gln		Thr214Pro
		+	Tyr203Pro		Gly205Asp Leu211Ala	4	Tyrzosser
38	Pro195Gly	+	Pro204Asn	÷		4	Asn212Glu
23	Thr202Gly		Gln200Glu		Gly205Asn	4	Gly213Gln
	Val197Gly	*		÷	Tyr208Ala	+	Asn212Ser
	Alal94Ser	+	Pro195Ser	*	Tyr203Ala	+	Ala209Asp
	Pro195Gln	+	Vall97Thr	+	Vall99Pro	+	Ala209His
40	Gly196Asn	+	Ser206Asp	÷	Leu211His	+	Thr214Ser
40	Vall97Asp	4	Tyr203His	+	Tyr208Cys	+	
	Ala194Gln	+	Pro195Asn	+	Ala209His	+	Ser210Asp
	Val199Ser	+	Gln200Ser	÷	Tyr203Asn	4	Ser206Asp
	Ala194Asn	+	Pro195Gin	÷	Ser206Glu	*	Gly213Ser
11.2	Pro195Ser	个		÷	Ser206Asp	÷	Gly213Gln
45	Ala194Gly	+	Vall99Thr	÷	Tyr208His	÷	Gly213Pro
	Ala194Pro	÷	Vall97Cys	÷	Gln200Asp	4	Pro204Gly
	Thr202Gln	+	Thr207Glu	+	Tyr208Cys	+	Leu211Pro
	Gly196Gln	+	Asn198Glu	4	Tyr203Gln	+	Gly205Pro
	Thr202Asn	÷	Tyr203Pro	÷	Gly205Ser	÷	Gly213Glu
50	Pro195Asn	*	Asn198Ser	+	Ala209Gly	÷	Leu211Thr
	Asn198Asp	÷	Gln2005er	÷		÷	Gly205Asn
	Pro195Gln	+	Vall99Gly	÷	Tyr203Asn	÷	Thr207Glu
	Ala194Gln	+	Thr202Gln	4		+	Tyr208His
	Ala194Ser	+	Pro204Asp	+	Thr207Pro	4	Tyr208Thr

	Asn198Gln	+	Val199Gln	+	Gln200Asn	4	Ala209Gln
	Ala194Glv	+	Asn198Ser	+	Pro204Asp	4	Ala209His
	Gly196Gln	÷	Vall97Thr	+	Ser206Glu	+	Ala209Pro
	Gln200Ser	+	Thr202Pro	٠.	Tyr203Thr	4	Thr207Gly
5	Ala194Thr	+	Val197Gly	÷	Gln200Asn	*	Thr207Asp
~	Val197Pro	į.	Vall99Asn	.j.	Gln200Glu	+	Leu211Ile
	Gly196Pro	+	Pro204Ser	÷	Ala209Ser	4	Leu211Gln
	Pro195Gly	+	Gly196Gln	4	Asn198Gln	+	Tyr208Glu
	Gln200Ser	+	Tyr203Met	+		+	
10	Ala194Gln	+	Pro195Glv		Gly205Glu		TyrZ08Asn
210				*	Ala209Gly	*	Ser210Glu
	Gly196Asn	+	Vall97Asn	4	Ser210Asp	+	Asn212Gln
	Gly196Gln	+	Thr2025er	÷	Gly2053er	4	Ser210Glu
	Gln200Asn	+	Gly205Pro	÷	Leu211Cys	4	Thr214Pro
	Ala194Ser	÷	Gly196Gln	÷	Thr2075er	+	Ser210Asp
15	Vall97Gln	+	Thr202Pro	÷	Tyr203Ala	4	Ser206Asp
	Gly196Gln	÷	Asn198Glu	+	Asn212Ser	-3-	Gly213Asn
	Pro195Asn	+	Vall97Gln	÷	Gly205Gln	4	Leu211Glu
	Thr207Glu	+	Tyr208Leu	÷	Leu211Met	÷	Gly213Gln
	Pro195Ser	4	Val197Pro	+	Pro204Glu	+	Leu211Cys
20	Pro195Gly	÷	Gly196Ser	÷	Val199Gln	4	Thr214Asp
	Vall97Asn	÷	Gly205Asn	÷	Thr207Ser	-}-	Ser210Asp
	Ala194His	+	Tyr203His	÷	Gly205Pro	4	Ser206Glu
	Pro195Asn	+	Asn198Gin	4	Vall99Gln	÷	Leu211Gln
	Vall97Pro	4	Thr202Gly	÷	Pro204Gly	+	Thr207Ser
25	Thr202Pro	4	Tyr203Leu	*	Leu2l1Ala	4	Thr214Asp
	Pro195Asn	+	Vall99His	÷	Tyr203Met	4	Thr207Glu
	Vall99Cys	÷	Pro204Gly	÷	Thr207Ser	+	Thr214Asp
	Ala194Ser	+	Pro195Gln	+	Tyr203Thr	4	Tyr208Pro
	Vall99Cys	4	Tyr203Cys	÷	Ser206Asp	4	Tyr208Ala
30	Vall97Thr	+	Thr202Gln	÷	Leu211Glu	÷	Asn212Ser
	Gly196Ser	+	Val199Pro	÷	Ala209Gln	÷	Leu211Asn
	Ala194Gly	÷	Ala209Gln	+	Asn212Asp	+	Thr214Gln
	Ala194Gln	÷	Thr207Asn	÷	Ala209Pro	÷	Leu211His
	Gly196Ser	+	Vall97Ser	Ť	Thr202Gln	÷	Leu211Gln
35	Ala194Thr	+	Vall97Ser	+	Thr202Pro	÷	Thr207Pro
	Gly196Pro	4	Thr202Pro	+	Gly205Glu	-3-	Gly213Pro
	Ala194Pro	+	Pro195Gly	+	Vall97Asn	4	Vall99Cys
	Thr202Gly	÷	Thr207Ser	÷	Tyr208Pro	4	Leu211Pro
	Thr202Asn	+	Pro204Asp	÷.	Thr207Ser	+	Gly213Asn
40	Gly196Gln	+	Vall97Cys	4	Tyr203Met	+	Ala209Asn
	Gly196Gln	4	Ser206Glu	4	Thr207Ser	4	Gly213Pro
	Pro195Ser	+	Vall99Cys	ተ	Ser210Glu	4	Asn212Ser
	Ala194Ser	-ş-	Ser206Asp	4	Asn212Ser	+	Thr214Gln
	Gly196Gln	÷	Gln200Ser	4	Thr202Gln	+	Ala2095er
45	Gly196Gln	4	Tyr203Thr	÷	Thr207Gln	4-	Asn212Glu
	Ala194Pro	÷	Thr202Gln	÷	Tyr208Cys	÷	Leu211Pro
	Gln200Asp	+	Tyr203Cys	÷	Leu211Gln	+	Asn212Gln
	Gly196Asn	4	Tvr203Met	÷	Leu211Asn	4	Gly213Asn
	Pro195Gln	4	Gly196Asn	+	Gln200Ser	+	Thr202Gln
50	Thr202Pro	+	Tyr203Gly	+	Asn212Ser	÷	Thr214Gly
	Gln200Asp	+	Tyr203Thr	喇	Pro204Gln	+	Gly205Ser
	Gly196Ser	of.	Thr202Pro	÷	Pro204Asn	÷	Ala209Ser
	Gly196Ser	+	Gln200Ser	+	Pro204Gly	+	Ser210Asp
	Ala194Gln	÷	Gln200Asn	4	Thr202Ser	+	Gly205Gln

	Pro195Gly	+	Gln200Asn	-ŧ-	Thr207Asp	÷	Ala209His
	Gln200Asn		Thr202Ser	4	Tyr203Ala	÷	Thr214Gly
	Gln200Glu	+	Ala209Pro	4	Leu21111e	+	Gly213Asn
	Ala194Asn		Thr202Ser	+	Tyr203Met	+	
5	Vall97Asn		Asn198Ser	4	Thr207Gln	÷	Thr214Glu
	Vall97Met	4	Gln200Ser	4	Pro204Glu	÷	Ala209Pro
	Gly196Asn		Val199Asn	-4-	Leu211Glu	+	Asn212Gln
	Pro195Gln		Thr202Gln	4	Gly205Asp	4	Tyr208Asn
	Thr202Pro		Ser206Asp	+	Leu21111e	4	Gly213Ser
10		4	Gln200Glu	+	Thr202Gln	4	Tyr208Met
	Asn198Glu	÷	Tyr203Thr	4	Tyr208Asn	4	Gly213Gln
	Asn198Ser	÷	Ser210Glu	+	Leu211His	÷	Thr214Pro
	Gly196Ser		Val197Gly	4	Pro204Glu	4	Thr214Ser
	Tyr203Met		Ser206Glu	+	Tyr208Ser	÷	Ala209His
15	Gly196Gln		Gln200Ser	4	Leu211Cys		
7.0	Ala194Gly		Val199Asn	4	Thr202Asn		Gly213Pro
	Asn198Ser		Thr202Asn	+	Tyr203G1v	+	Ser210Glu
	Vall99Gln	+	Gln200Ser				
	Thr202Gln			+	Tyr203His	÷	Thr214Asp
20			Ser206Asp	*	Thr207Ser	*	
20	Alal94Thr	+	Tyr203Gln	÷	Thr207Asp	+	Leu211Ile
	Ala209Ser		Ser210Asp	+	Asn212Gln	*	Gly2135er
	Vall97Ser		Tyr203Gly	÷	Ser206Glu	+	Asn212Gln
	Ala194Ser	+	Asn198Ser	÷	Gly205Gln		Ser210Asp
00	Ala194Gln	+	Pro195Ser	*		+	Pro204Asn
25	Ala194Gly	+	Asn198Ser	+	Ala209Glu	4	Thr214Asn
	Vall99Met		Ser206Asp				
	Thr202Gln		Gly205Ser	4	Leu211Asp		Asn212Glu
	Pro195Ser		Ala209Gly			+	Thr214Asp
30			Thr207Pro				
30	Ala194Ser				Ala209Glu		
	Gin200Ash Gin200Ser		Thr202Gln			*	Ser210Glu
		+				+	Asn212Gln
			Ala209Asp				Asn212Gln
35	Pro204Gly		Leu211Gln			+	
33	Tyr203Gly			*	Gly205Glu		
			Pro204Glu		Gly205Asp	+	
	Thr202Gly		Pro204Asp	4-		÷	
	Val199Gly		Ser210Asp		Leu211Asp		
40	Gly196Pro	+	Thr202Ser	+		÷	Ser206Glu
40	Vall97Thr		Gly205Asp	*	Ser206Glu	+	Gly213Gln
	Pro204Asn		Gly205Glu	+	Ser206Glu	Ť	
	Alal94His		Gly205Asp	+	Ser206Asp		Leu211His
	Pro195Asn		Ser206Glu	4	Thr207Asp		Asn212Ser
		÷		÷		+	Leu211Gly
45	Gly196Gln	+	Pro204Asn	÷		*	Thr207Glu
	Ala194Thr	+	Vall97Cys	+		4	Thr207Asp
	Ala194Pro	4	Tyr208Asp	*	Ala209Asp	÷	
	Gln200Asp			+		÷	
	Vall99Asn	+	Gln200Asp		Thr202Gln	÷	
50	Ala194Ser	+		÷	Thr202Gly	ተ	
	Val199Cys	4		*		+	
	Ala194Gln		Val197Asp	+	Tyr208Gln		
	Pro195Gly		Asn198Glu		Ser210Asp		Leu211Gln
	Ala194Pro	÷	Pro195Asn	+	Asn198Asp	÷	Ser210Asp

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Prol95Gln	4	Asn198Glu	+	Vall99Ser	+	Ser210Asp	
Vall97His	*	Asn198Glu	4	Thr207Pro	4	Ser210Asp	
Gly196Pro	ተ	Val197Gly	÷	Asn198Asp	÷	Ser210Glu	
Asnl98Glu	÷	Ala209Gln	+	Leu211Glu	÷	Thr214Pro	
Gln200Glu	4	Tyr203Asn	÷	Thr207Gln	4	Ala209Glu	
Pro195Ser	4	Gly196Ser	+	Gln200Glu	÷	Ala209Asp	
Pro1955er	4	Gln200Asn	4	Ala209Glu	+	Langillala	

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10
                   Loop 6 - Quintuple Mutation Variants
    Val197Ala + Asn198Gln + Thr207Ser + Tyr208Ile + Asn212Asn
    Alai94Glv + Glv196Ser + Vall97Glv + Gln200Glv + Leu211Glv
    Gln200Asp + Thr202Ser + Tvr203Ser + Pro204Ser + Asp212Ser
    Pro195Ser + Val199Ala + Glv205Asn + Ser206Glu + Glv213Ser
15
    Val199His + Pro204Asp + Gly205Pro + Leu211Gly + Thr214Ser
    Ala194Glv + Thr207Pro + Ser210Glu + Leu211Cvs + Glv213Gln
    Pro195Asn + Glv196Pro + Asn198Ser + Thr202Gly + Glv213Asn
    Gly196Ser + Val197Gln + Pro204Ser + Gly205Asp + Leu211Gly
    Pro195Ser + Gly196Gin + Pro204Asn + Gly213Asp + Thr214Gly
20
    Pro195Glv + Val199Asn + Gln200Asn + Ser210Glu + Leu211Glv
    Val197Ser + Val199Glv + Tvr203Thr + Glv205Ser + Asn212Glu
    Pro195Asn + Asn198Asp + Thr202Ser + Ala209His + Asn212Gln
    Gly196Asn + Gly205Pro + Thr207Pro + Asn212Asp + Gly213Gln
    Val197Gly + Asn198Asp + Val199His + Gly205Gln + Tyr208His
25
     Tvr203Val + Thr207Glv + Ala209Ser + Asn212Glu + Glv213Gln
    Ala194Thr + Pro195Gly + Gly196Ser + Tyr203Asn + Asn212Ser
    Pro195Gln + Thr202Glv + Tvr203Leu + Pro204Glv + Ser210Asp
    Pro195Asn + Val199Ala + Thr202Asn + Tyr208Pro + Ser210Asp
    Ala194Pro + Pro195Gly + Asn198Glu + Pro204Asn + Tyr208Pro
    Alal94Ser + Val197Thr + Asn198Ser + Thr202Pro + Asn212Ser
30
    Gly196Ser + Val199Pro + Thr207Ser + Tyr208Thr + Asn212Gln
    Gly205Glu + Tyr208Gly + Leu211Ile + Asn212Ser + Thr214Gly
     Gln200Ser + Thr202Gly + Thr207Asp + Leu211Ser + Thr214Gln
     Pro195Asn + Thr207Asp + Tvr208Asn + Asn212Ser + Gly213Asn
35
     Pro195Asn + Tvr203Ser + Pro204Glu + Leu211Val + Asn212Gln
     Gln200Asp + Gly205Ser + Tyr208Met + Leu211Asn + Asn212Ser
    Ala194Ser + Val199Pro + Gly205Glu + Tyr208Met + Gly213Ser
    Asni98Ser + Gln200Glu + Thr202Glv + Ala209Gln + Leu211Asn
     Glv196Pro + Asn198Glu + Thr202Ser + Ala209Thr + Thr214Gly
     Ala194Gln + Pro195Gly + Gly196Asn + Tyr203Ile + Thr214Pro
40
     Pro195Gln + Val197Cys + Thr202Gln + Tyr203Cys + Tyr208His
     Vall99Pro + Pro204Gly + Gly205Ser + Thr207Ser + Gly213Asp
     Tyr203Gly + Pro204Ser + Gly205Asn + Ala209Thr + Ser210Asp
     Ala194Ser + Thr207Ser + Tyr208Cys + Leu211Pro + Thr214Pro
     Pro195Gly + Vall99His + Gly205Glu + Ala209Asn + Leu211Pro
45
     Pro204Asn + Tyr208Ile + Ala209Gly + Leu211Gln + Gly213Glu
     Alal94Gln + Val197Cys + Asn198Ser + Pro204Gly + Asn212Glu
     Asn198Glu + Pro204Asn + Ala209Thr + Leu211Ser + Gly213Pro
     Glv196Ser + Val199Ser + Pro204Asp + Thr207Glv + Tvr208Ile
     Gln200Glu + Thr202Ser + Tyr203Ala + Pro204Gly + Tyr208Met
50
     Asn198Gln + Thr202Pro + Gly205Asn + Thr207Glu + Thr214Pro
     Glv196Ser + Vall99Pro + Ala209Gln + Ser210Asp + Leu211Asn
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	Ala194Gly	÷	Thr207Asn	÷	Ala209Gln	÷	Asn212Asp	÷	Thr214Gln
	Pro195Gly	÷	Asn1986ln	÷	Vall99Thr	÷	Tyr208His	*	Leu21111e
	Ala194Pro	+	Thr202Gly	÷	Thr207Ser	÷	Tyr208Pro	÷	Leu211Pro
	Gly196Ser	4	Vall97Ala	÷	Gln200Asn	+	Thr202Pro	4	Ser210Glu
S	Val197Gln	4	Thr202Asn	+	Tyr203Asn	+	Gly205Asp	4	Tyr208Ala
•	Gly196Pro	+	Tyr203Ile	+	Pro204Asn	4	Leu211Ala	+	Thr214Gln
	Ala194Asn	÷	Gln200Asn	÷	Pro204Gln	4	Ala209Thr	+	Gly213Ser
	Ala194His	4	Pro195Gly	4	Gln200Ser	÷.	LeuZllAsn	4	Asn212Ser
	Ala194Ser	+	Glv196Ser	+	Gln200Asn	+	Ser206Asp	4	Thr207Gly
10	Gly196Asn	+	Tyr203Asn	+	Tyr208Ala	+	Ala209Pro	+	Gly213Gln
£U.		4		+				4	
	Ala194Thr		Vall99Asn		Tyr203Ser	*	Tyr208His		AsnZlZAsp
	Val197Glu	+	Vall99Ala	*	Tyr208Gln	+	Ala209Gly	*	Leu211Val
	Gln200Asn	+	Thr202Ser	+	Tyr203Ala	+	Thr207Gln	÷	Thr214Gly
	Vall97Asn	÷	Asn198Ser	ą.	Thr202Pro	÷	Thr207Gln	÷	Thr214Glu
15	Pro195Gln	+	Asn198Glu	+	Gln200Ser	+	Tyr203Cys	+	Gly213Gln
	Gly196Gln	÷	Asn198Ser	÷	Thr202Asn	÷	Tyr203Ser	+	Gly205Pro
	Ala194Thr	÷	Thr207Pro	÷	Tyr2081le	÷	Ala209Pro	÷	Thr214Asn
	Asn198Ser	÷	Vall99Fro	4	Thr202Asn	÷	Tyr203Gly	+	Asn212Glu
	Ala194Asn	÷	Thr202Asn	+	Ser210Asp	+	Leu211Val	÷	Asn212Ser
20	Vall97Ser	+	Vall99His	÷	Thr202Asn	÷	Ser210Asp	+	Leu211Cys
	Gly196Pro	4	Vall97Cys	4	Vall99Met	÷	Tyr203Ser	4	Leu211Asn
	Ala194Gly	+	Gly196Pro	4	Val199His	+	Thr202Pro	4	Ser210Glu
	Gly196Ser	+	Val197His	÷	Asn198Glu	+	Thr202Pro	4	Asn212Ser
	Ala194His	+	Gly196Asn	4	Vall97Gln	+	Thr202Ser	÷	G1y205G1u
25	Pro195Gly	÷	Glv196Pro	÷	Asn198Ser	4	Gln200Ser	4	Thr202Pro
	Vall97Asn	4	Asn198Asp	4	Gln200Asn	÷	Thr202Gln	+	Tyr208Ala
	Pro195Asn	4	Thr202Ser	÷	Pro204Asp	+	Tyr208Ala	4	Ala209Ser
	Tyr203His	+	Pro204Asn	÷	Gly205Asp	+	Thr207Gln	4	Leu211Gly
	Ala194Asn	4	Pro195Gin	÷	Gly196Gln	+	Pro204Asn	+	Gly213Glu
30	Vall97Thr	4	Vall99His	÷	Ser206Glu	+	Gly213Asn	4	Thr214Asn
	Gly196Gln	4	Val197Asn	4	Tvr203Thr	÷	Pro204Ser	4	Thr214Asp
	Gly196Asn	+	Val199Gly	÷	Gin200Ser	4	Tvr203Asn	4	Gly213Glu
	Ala194Thr	+	Gln200Asn	÷	Thr202Ser	+	Glv205Gln	+	Gly213Asp
	Pro1955er	+	Asn198Ser	+	Val199Gly	+	Tyr203Val	4	Thr207Glu
35	Ala194Asn	4	Pro195Gly		Thr202Gly	+	Tyr203Gly		Leu211Asp
0.0	Pro195Ser	+	Vall97Ser	4	Tyr203Cys	4	Gly205Glu	+	Ala209Thr
	Gly196Gln	+	Vall97Gly	+	Gly205Ser	4	Tyr208Leu	ų.	Thr214Asp
	Ala194Gln	4	Gly196Asn	4	Tyr203Pro	4	Pro204Ser	÷	Gly213Asp
	Gly196Gln	4	Thr202Gly	į.	Tyr203Cys	+	Pro204Gln	4	Ser206Glu
40	Vall97Pro	+	Vall99Met	÷	Tyr203Val	+	Pro204Glv	+	Thr214Asp
403	Gly196Pro	+	Gln200Asn	4	Tyr203Cvs	+	Ala209Thr	4	Thr 214Asn
	Asn198Gln	+	Pro204Asn	4	Thr207Gln	4	Glv213Pro	+	Thr214Asp
		+	Vall97Ser	+	Val199Ala	+	Thr207Asp	+	Leu211Gly
	Pro195Gly Pro195Gln	+	Asn198Gln	÷	Ser206Asp	÷	Thr207Ser	+	Ala209Ser
45						4	Ser210Asp	ų.	Thr214Ser
45	Ala194Ser	+	Tyr203Leu	+	Ala209Asn				
	Val199His	+	Thr202Ser	ą.	Gly205Asn	÷	Leu211Pro	·į.	Asn212Gln
	Gly196Ser	+	Asn198Ser	*	Thr207Asn	+	Tyr208Gln	-Ę-	Ser210Glu
	Pro195Asn	*	Asn198Gln	÷	Thr2075er	*	Gly213Asn	*	Thr214Gly
	Gly196Gln	+	Gln200Ser	*	Pro204Asn	*	Gly205Gln	+	Gly213Asp
50	Pro204Asn	4	Ser206Glu	*	Tyr208Leu	+	Ala209Gly		Asn212Gin
	Vall97Thr	+	Vall99Gly	+	Gln200Asp	+	Thr202Pro	÷	Thr207Gly
	Pro195Gln	4	Vall99Ser	4	Thr202Asn	+	Gly205Asp	+	Ala209Gln
	Gly196Gln	*	Tyr203Thr	+	Tyr208Cys	*	Leu211Ala	÷	Thr214Glu
	Asn198Gln	+	Gln200Ser	+	Pro204Gln	+	Asn212Ser	÷	Gly213Pro

	Vall97Pro	+	Vall99Asn	÷	Thr202Gln	+	Tyr203Asn	4	Gly213Ser
	Ala194Ser	+	Gln200Ser	4	Thr202Gln	÷	Thr207Gln	4	Ala209Glu
	Thr202Gly	4	Tyr203Thr	+	Tyr208Pro	+	Gly213Asp	+	Thr214Glu
	Val197Gln	+	Pro204Glv	4	Gly205Ser	4	Ala209Glu	4	Ser210Asp
5	Ala194Ser	÷	Val199Ala	4	Tyr208Ala	÷	Ala209Glu	+	Ser210Glu
	Val199Ala	4.	Gln200Ser	+	Glv205Pro	+	Asn212Glu	4	Gly213Asp
	Ala194Pro	+	Thr202Ser	+	Pro204Glu	÷	Gly205Asp	4	Ala209Pro
	Pro204Glu	÷	Gly205Glu	4-	Thr207Gly	ij.	Tyr208Ser	+	Leu211Ile
	Pro195Gln	+	Vall97Thr	4	Pro204Glu	+	Gly205Asp	4	Leu211Val
10	Vall99His	+	Gly205Asp	+	Ser206Glu		Ala209Gln	4	Asn212Gln
•	Tyr203Ala	+	G1y205G1u	+	Ser206Asp	+	Tyr208Ile	+	Asn212Gln
	Pro195Asn	4	Glv205Glu	4	Ser206Asp	4	Tyr208Ser	4	Ala209Ser
	Val197His	+	Pro204Gly	+	Gly205Glu	4	Ser206Asp	4	Tyr208Cys
	Thr202Asn	+	Pro204Ser	+	Gly205Asp	+	Ser206Asp	+	Tvr208Thr
15	Ala194Asn	+	Thr202Ser	4	Tyr203Gly	+	Ser206Glu	4	Thr207Glu
***	Pro195Ser	+	Gly196Gln	+	Vall99Thr	÷	Ser206Glu	+	Thr207Asp
	Gly196Pro	+	Ser206Asp	4	Thr207Glu	4	Tyr208Thr	+	Leu211His
	Ala194His	4	Gly196Gln	÷	Pro204Asn	÷	Tyr208Asp	4	Ala209Asp
	Val199Ala	÷	Tvr203Pro	+	Tyr208Asp	+	Ala209Asp	4	Asn212Gln
20	Vall99Ala	+	Thr202Ser	+	Thr207Glu	+	Tyr208Asp	4	Thr214Ser
20	Gly196Asn	4	Thr202Gln	+	Pro2045er	,	Thr207Asp	+	Tyr208Asp
	Pro195Gln	+	Gln200Glu	+	Thr202Pro	+	Tyr203Pro	4	Ser210Asp
	Gly196Pro	+	Val197Thr	+	Asn198Gln	*	Gln200Asp	4	Ser210Asp
	Gly196Gln	+	Asn198Glu	+	Thr207Pro	+	Tyr208Ser	4	Ser210Glu
25	Ala194Pro	4	Asn198Glu	+	Thr207Pro	+	Ala209His	4	Ser210Glu
23	Asn198Glu	+	Vall99Gln	+	Pro204Ser	4	Tyr208Asn	4	Ser210Asp
	Pro195Glv	4	Asn198Glu	4	Thr207Gly	4	Tyr208Cys	+	Ser210Asp
	Asn198Asp	T +	Vall99Thr	+		+		+	
	Glv196Pro	4	Asn198Gln	+	Leu211Asp Gln200Glu	÷	Asn2125er Tyr203Asn	4	Thr214Gly Ala209Glu
30	Gly196Pro	÷	Tyr203Thr	+	Pro204Asp	*	Ser206Asp	4	Ala209Glu
30	Pro195Asn	+	Gly196Pro	+	Asn198Asp	+	Ala209Pro	4	Asn212Glu
	Pro195Asn	+	Gly196Gln	+	Gly205Asp	+	Thr207Glu	+	Leu211Thr
	Thr202Asn	4	Pro204Asp	+	Thr207Asp	÷	Tyr208Met	+	Thr214Pro
	Tyr203Glv	*	Pro204Asp	4	Thr207Asp	÷	Asn212Gin	÷	Thr2146ly
35	Pro195Ser	+	Tyr203His	4	Pro204Glu	+	Thr207Asp	+	Gly213Gln
33	Asn198Glu	4	Gln200Glu	4	Tyr203Cys	4	Pro204Gly	j.	Asn212Gln
	Vall97Glu	4	Vall99Glv	+	Thr202Glv	+	Tyr203Ser	+	Gly213Glu
	Pro204Gly	+	Thr207Asn	4	Ala209His	4	Ser210Asp	4	Asn212Asp
	Pro195Gly	4	Gly196Gln	4	Thr202Gln	4	Ser210Asp	4	Asn212Asp
40	Thr202Asn	4	Tyr203Asn	4	Gly205Pro	+	Ser210Asp	4	Asn212Asp
40	Thr202Gln	4	Tyr203Gln	÷	Ser210Asp	÷	Asn212Asp	4	Gly213Gln
	Gly196Ser	4	Ser210Asp	÷	Leu211Gly	*	Asn212Asp	4	Thr214Gln
	Gly196Pro	+	Ala209Ser	+	Ser210Glu	4	Leu211Asn	4	Asn212Asp
	Gly205Ser	+	Ala209Pro	4	Ser210Glu	+	Asn212Asp	+	Thr214Pro
45	Pro195Gly	+	Tyr203Gly	4	Ser210Asp	+	Asn212Asp	4	Thr214Ser
43	Pro195Gln	4	Vall97Asn	4	Vall99Cvs	+	Tyr208Glu	4	Ser210Asp
	Vall97Ser	+	Tyr203Gly	+	Pro204Glu	+	Thr207Ser	4	Tyr208Asp
	Pro195Ser	+	Gly196Asn	4	Val197Asp	+	Vall99Gly	+	Ser210Glu
	Glv196Pro	+	Vall97Asp	+	Thr202Pro	+	Ser210Glu	4	Thr214Pro
50	Vall97Glu	+	Vall99His	+	Tyr208Thr	4	Leu21161n	+	Thr214Glu
30	Asn198Asp	4	Vall99Asn	+	Thr207Asn	+	Ala209His	÷	Gly213Asp
	Vall97His	7	Asn198Glu	4	Tyr203Gln	+	Tyr208Cys	4	Gly213Asp
		マヤ	Vall97Asn	+	Asn198Glu	+	Thr202Pro	4	Gly213Asp
	Pro195Asn Pro195Ser	+	Asn198Glu	+	Tyr203Ser		Glv205Ser	÷	AlaZ09Asp
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Pro195Gly + Gly196Asn + Asn198Asp + Val199Met + Ala209Glu Pro195Gln + Asn198Glu + Thr202Asn + Pro204Glv + Ala209Asp Valia7Glu + Gln200Glu + Thr202Gly + Tyr208Ala + Gly213Gln Val197Asp + Gln200Asp + Thr207Ser + Tyr208Ile + Ala209Ser Val197Asp + Gln200Glu + Ala209Ser + LeuZllGly + Asn212Ser 5 Val197Glu + Gln200Asp + Thr202Asp + Glv205Gln + Asn212Gln Ala194Pro + Gly196Pro + Val197Met + Gln200Glu + Asn212Asp Glv196Gln + Gln200Glu + Thr202Pro + Tvr203Tle + Asn212Glu Alal94His + Gln200Asp + Asn212Glu + Glv213Pro + Thr214Asn Vall99Pro + Gln200Glu + Pro204Gly + Asn212Glu + Glv213Ser 10 Asn198Ser + Gln200Asp + Gly205Pro + Thr207Ser + Asn212Glu Alal94Asn + Gln200Asp + Glv205Asn + Tvr208Asn + Asn212Asp Pro195Asn + Gln200Ser + Thr202Pro + Pro204Asp + Ala209Glu Pro195Ser + Thr202Asn + Tyr203Cys + Pro204Glu + Ala209Asn Ala194His + Asn198Ser + Thr202Asn + Pro204Glu + Ala209Asp 15 Ala194His + Pro204Asn + Ser206Glu + Ala209Glu + Thr214Ser Pro195Gly + Val197Cys + Ser206Glu + Ala209Glu + Asn212Ser Thr202Glv + Ser206Glu + Thr207Ser + Tyr208Met + Ala209Glu Ala194Gly + Gln200Glu + Thr207Asp + Leu211Ser + Thr214Pro Pro195Asn + Val199Ser + Gln200Glu + Glv205Asn + Thr207Asp Alal94Gln + Asn198Gln + Glv205Pro + Ser210Asp + Glv213Asp Glv196Ser + Thr207Glv + Ser210Glu + Leu211Thr + Glv213Asp Asn198Gln + Pro204Gln + Thr207Asp + Tvr208Thr + Ser210Glu Ala194Ser + Glv196Gln + Thr207Glu + Ser210Glu + Leu211Thr 25 Thr207Glu + Ser210Glu + Asn212Ser + Gly213Ser + Thr214Ser Vall97Cys + Thr207Glu + Ala209His + Ser210Glu + Asn212Ser Asn198Glu + Val199Met + Tyr208Ala + Gly213Gln + Thr214Asp Ala194Gln + Asn198Glu + Ala209Pro + Leu211His + Thr214Asp Asn198Asp + Thr207Pro + Leu211Glv + Asn212Ser + Thr214Asp Ala194Ser + Gly196Asn + Asn198Asp + Pro204Gln + Thr214Glu 30

TABLE 28

Loop 6 - Sextuple Mutation Variants Alai94Gln + Vall97Ser + Thr202Ser + Tyr203Ser + Ala209Ser + Asn212Asn Pro195Ser + Vall99Cys + Gly205Ser + Leu211Thr + Asn212Glu + G1v213Pro Vall97Thr + Asn198Ser + Vall99Pro + Gln200Ser + Thr202Ser + Leu211Asn 40 Thr202Gly + Pro204Ser + Gly205Asn + Tyr208Asp + Gly213Gln + Thr214Pro Val197Gly + Glm200Glu + Thr202Gly + Tyr208Ala + Leu211Val + Asn212Ser Ala194Pro + Gly196Ser + Vall99Cys + Tyr203Ala + Pro204Ser 45 + Ala209Asp Pro195Asn + Val199Pro + Thr202Asn + Tvr203Gly + Thr207Asp + Glv213Asn Alai94Gln + Thr202Ser + Tyr203Tle + Pro204Asn + Gly205Asp + Tvr208Ser Ala194Gln + Val197His + Ala209Ser + Ser210Asp + Leu2l1Gly + Asn212Gln Thr202Gly + Gly205Pro + Ser210Asp + Leu211Ala + Gly213Ser

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+ Thr214Gln
    Alai94His + Gln200Ser + Thr202Glv + Pro204Ser + Tvr208His
      + Gly213Glu
    Ala194Asn + Pro195Gln + Glv205Asn + Tyr208Ser + Leu211Val
5
      + Thr214Pro
    Gly196Pro + Asn198Ser + Gln200Ser + Thr202Asn + Tyr208Ile
      + Thr214Glu
    Pro195Asn + Gly205Pro + Thr207Gln + Ser210Glu + Leu211Asn
      + Glv2l3Pro
   Ala194Ser + Val197Glv + Asn198Aso + Tvr203Cvs + Glv205Gln
      + Leu211Met
    Alal94Ser + Val197Asp + Val199Gln + Tvr203Cvs + Glv205Ser
      + Gly213Gln
    Ala194Pro + Thr202Glv + Thr207Ser + Tvr208Met + Leu211Pro
      + Gly213Glu
15
    Ala194Thr + Pro195Asn + Gly196Gln + Gln200Ser + Thr202Asn
      + Pro204Glu
    Ala194Gln + Gly196Asn + Val197Ser + Asn198Ser + Val199Thr
      + Ser210Glu
    Gly196Ser + Val199Gly + Tyr203Ile + Pro204Asn + Leu211Asp
      + Thr214Gln
    Ala194Asn + Gln200Asn + Pro204Gln + Ala209Thr + Leu211Asn
      + Glv213Ser
    Ala194His + Pro195Glv + Glv196Asn + Gln2005er + Tvr203Ser
25
      + Asn212Ser
    Ala194Pro + Val197Met + Val199Asn + Thr202Ser + Ser206Asp
      + Thr207Asn
    Pro195Gln + Thr202Pro + Glv205Asn + Ala209Pro + Asn212Ser
      + Thr214Asn
    Pro195Asn + Asn198Glu + Vall99His + Pro204Asn + Thr207Gly
      + Leu211Met
    Glv196Ser + Pro204Asn + Thr207Pro + Asn212Asp + Glv213Ser
      + Thr214Pro
    Ala194Ser + Pro195Ser + Val197Cys + Pro204Asn + Thr207Glu
35
      4 Glv213Gln
    Alai94His + Pro195Glv + Val197Glv + Val199Gln + Thr207Glv
      + Asn212Glu
    Ala194Gln + Pro195Ser + Val197Ser + Tyr203Met + Leu211Glu
      + Glv213Asn
    Ala194Asn + Gly196Asn + Pro204Asp + Thr207Pro + Tyr208Ser
40
      + Thr214Ser
    Pro195Asn + Thr202Gly + Gly205Asp + Thr207Gln + Tyr208Thr
       + Ala209Asn
    Alal94His + Pro195Gly + Vall97His + Gly205Gln + Ala209Glu
45
      + Thr214Asn
    Ala194Gin + Asn198Gin + Tyr203Met + Ala209Gin + Ser210Glu
       + Leu2l1Gly
    Alai94Pro + Gly196Ser + Gln200Ser + Thr202Pro + Thr207Asp
       + Ala209Gly
50 Pro195Gln + Gly196Ser + Asn198Gln + Gly205Ser + Ser210Asp
       + Leu211Val
    Asn198Gln + Val199Met + Gln200Glu + Thr202Gly + Gly205Asn
      + Tvr208Ala
    Ala194Pro + Val199Ala + Pro204Asn + Thr207Gln + Leu211Glu
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+ Gly213Ser
   Gly196Pro + Val197Thr + Val199His + Gly205Asn + Ser206Asp
      + Thr207Asn
   Pro195Asn + Gly196Ser + Thr202Asn + Tyr203Gly + Leu211Asn
      + Asn212Glu
   Ala194Ser + Pro195Gin + Val197Cys + Ser206Glu + Tyr208His
      + Asn212Gln
   Pro195Gln + Gly196Pro + Val197Thr + Ser210Asp + Gly213Ser
      + Thr214Pro
   Alai94Gly + Pro195Ser + Thr202Gly + Pro204Glu + Tyr208Thr
10
      + Gly213Pro
   Ala194Asn + Pro195Asn + Gly196Asn + Gly205Pro + Ala209Asn
      + Ser210Asp
   Pro195Ser + Val199Gln + Tyr208Asn + Ala209Gln + Leu211Gly
15
      + Gly213Gln
   Asn198Asp + Val199Ala + Thr202Asn + Ala209Pro + Asn212Gln
      + Thr214Gly
    Pro195Asn + Gly196Gln + Vall99Pro + Ser206Glu + Tyr208Ala
      + Leu211Val
   Alal94Gln + Pro195Ser + Asn198Asp + Val199Ser + Thr202Pro
20
      + Ala209Gln
    Pro195Gly + Val199Met + Gly205Glu + Thr207Asn + Ala209Pro
      + Gly213Pro
    Pro195Asn + Gly196Gln + Gln200Asp + Thr207Asn + Ala209Gly
25
      + Asn212Ser
    Gly196Gln + Val197His + Thr207Asn + Ser210Asp + Leu211Ala
      + G1v213Gln
    Alai94Gly + Val197Thr + Tyr203Met + Gly205Glu + Ala209Gly
      + Thr214Glv
    Gln200Glu + Thr202Asn + Tyr203Gly + Thr207Asn + Asn212Gln
      + Glv213Pro
    Glv196Asn + Thr202Ser + Pro204Glu + Leu211Pro + Gly213Ser
      + Thr214Asn
    Pro195Gly + Vall97Asn + Vall99Gln + Gln200Asn + Thr207Gly
      + Asn212Ser
35
    Pro195Gln + Gly196Pro + Val197His + Tyr203Gly + Ser206Asp
      + Thr214Ser
    Gly196Gln + Tyr203His + Thr207Asn + Leu211Asn + Gly213Pro
       + Thr214Asp
    Ala194Asn + Asn198Ser + Gin200Asn + Thr202Ser + Tyr203Ile
40
      + Ala209Thr
    Alal94His + Vall97Cys + Gln200Ser + Tyr203Gly + Thr207Gly
       + Ala209His
    Asn198Gln + Vall99Thr + Sln200Asp + Pro204Asn + Asn212Ser
      + G1y213Gln
45
    Gly196Pro + Tyr203Gln + Pro204Ser + Thr207Asn + Tyr208Met
      + Leu211Asp
    Gly196Ser + Val197Met + Asn198Ser + Thr202Asn + Thr207Asp
       + Asn2126ln
    Pro195Glv + Glv196Pro + Thr202Asn + Tyr203Ile + Gly213Asp
      + Thr214Asn
    Pro195Gly + Gly196Pro + Glm200Glu + Pro204Ser + Tyr208Tle
      + Gly213Ser
    Val199Ala + Thr202Glo + Gly205Ser + Ala209Asn + Ser210Glu
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+ Leu211Cvs Ala194His + Pro195Ser + Vall99Thr + Gln200Glu + Tyr203Fro + Tvr208Cvs Gly196Gln + Pro204Gly + Ser206Asp + Thr207Pro + Ala209Gln + Glv213Ser Pro195Asn + Thr202Asn + Pro204Asn + Ala209Gln + Asn212Asp + Gly213Gln Gly196Ser + Asn198Gln + Tyr203His + Asn212Ser + Gly213Asp + Thr214Gly 10 Ala194Gln + Val197Pro + Val199Gln + Gln200Asn + Tyr208Glu + Thr214Ser Vall99Cys + Gin200Asn + Pro204Gly + Ser206Asp + Thr207Ser + Asn212Ser Alal94Gln + Glv196Gln + Val199His + Thr202Pro + Tyr203Thr 15 + Gly205Ser Asn198Gln + Val199Gly + Thr202Ser + Ser210Asp + Asn212Ser + Gly213Gln Val199Thr + Gln200Asn + Pro204Ser + Tyr208Val + Asn212Gln + Thr214Asp 20 Alal94His + Gly196Gln + Val199Gln + Thr202Gly + Pro204Asp + Leu211Cys Ala194Ser + Val197Gly + Pro204Gln + Ala209Pro + Ser210Glu + Thr214Gly Alai94Gln + Gly196Pro + Tyr203Gln + Thr207Pro + Tyr208Pro 25 + Ala209Asn Gly196Ser + Thr202Asn + Tyr208Ile + Ala209Gln + Leu211Ala + Glv213Glu Pro195Asn + Glv196Pro + Val197Glu + Gln200Asn + Tyr203Ser + Tyr208Ser Gly196Ser + Val199His + Gly205Asp + Tyr208Val + Ala209Gly + Thr214Pro Val197Ser + Val199Met + Gln200Asn + Thr202Ser + Tvr208Cys + Gly213Gln Ala194Ser + Glv196Gin + Val199Pro + Leu211Val + Glv213Glu 35 + Thr214Glv Ala194Gln + Asn198Gln + Val199Cys + Thr207Gly + Leu211Asp + Asn212Glu Ala194Thr + Asn198Gln + Thr202Asn + Pro204Ser + Gly213Glu + Thr214Asp Alai94Thr + Pro195Ser + Vali99Ala + Ala209Glu + Ser210Glu 40 + Leu211Cvs Tyr203Leu + Gly205Ser + Ala209Glu + Ser210Glu + Asn212Ser + Glv213Asn Val197Glu + Asn198Glu + Tyr203Pro + Thr207Gly + Ala209Ser + Asn212Ser 45 Val197Asp + Asn198Asp + Val199His + Thr202Ser + Pro204Gln + Ala209Asn Gly196Asn + Vall97Glu + Asn198Asp + Gln200Ser + Pro204Asn + Thr207Glv Pro195Gln + Thr202Ser + Tyr203Ser + Thr207Gln + Asn212Asp + Gly213Glu Glv196Gln + Tyr203His + Gly205Ser + Leu211Asn + Asn212Asp + Gly213Glu Asn198Ser + Gly205Ser + Tyr208Ile + Asn212Glu + Gly213Glu

+ Thr214Pro Alai94Ser + Glv196Gin + Pro204Glu + Glv205Asp + Tvr208Asp + Thr214Asn Alal94Ser + Pro195Glv + Val199Cvs + Pro204Asp + Glv205Glu + Asn212Gln Ala194Thr + Val199Pro + Glv205Asn + Ala209Gln + Ser210Glu + Leu211Asp Thr202Gln + Thr207Gly + Ser210Asp + Leu211Glu + Gly213Gln + Thr214Ser 10 Thr202Gln + Gly205Asp + Ser206Glu + Tyr208Met + Gly213Gln + Thr214Asn Ala194Glv + Glv205Glu + Ser206Glu + Ala209Glv + Leu211Gln + Thr214Glv Gln200Ser + Thr202Ser + Tyr203Glv + Gly205Asp + Ser206Glu + Thr214Gln 15 Val197Asn + Thr202Ser + Gly205Glu + Ser206Glu + Ala209His + Thr214Ser Alal94Gln + Thr202Ser + Tyr203Glv + Ser206Asp + Thr207Glu + G1v213Ser Gly196Pro + Val199Gln + Tyr203Met + Ser206Glu + Thr207Asp 20 + Ala209Thr Pro195Gly + Gly196Pro + Thr202Ser + Pro204Gln + Tyr208Asp + Ala209Glu Pro195Gln + Gly196Pro + Vall97Pro + Gln200Asp + Gly205Ser 25 + Ser210Asp Gly196Ser + Asn198Glu + Gly205Pro + Ala209His + Ser210Glu + Asn212Gln Ala194Thr + Asn198Asp + Thr202Ser + Tyr203Cys + Ala209Pro + Ser210Glu 30 Gly196Pro + Asn198Glu + Gly205Ser + Ser210Glu + Leu211Asn + Thr214Asn Alai94Pro + Gly196Ser + Asn198Glu + Gly205Ser + Thr207Pro + Ser210Glu Gly196Ser + Val197His + Asnl98Asp + Gln200Ser + Thr207Gln 35 + Ser210Asp Asn198Glu + Val199Met + Gly205Pro + Ala209His + Ser210Glu + Thr214Pro Val197Ser + Asn198Glu + Pro204Ser + Thr207Ser + Ala209Pro + Leu211Asp Pro195Ser + Gln200Asp + Thr202Asp + Tvr203Ser + Ala209Asp 40 + Asn212Ser Gln200Asp + Pro204Ser + Gly205Pro + Tyr208His + Ala209Asp + Leu211Asn Pro2045lu + Ser206Asp + Tvr208Ile + Leu211Glv + Asn212Gln + Thr214Asn 45 Glv196Ser + Asn198Ser + Vall99Ala + Pro204Asp + Ser205Glu + Tyr208Ser Pro195Asn + Pro204Asp + Ser206Asp + Tvr208Ser + Leu211Ser + Asn212Gln Ala194Glv + Asn198Glu + Gln200Ser + Thr207Glv + Ala209Asn + Asn212Glu Asn198Glu + Gly205Gln + Ala209Pro + Leu211Cys + Asn212Asp + G1v2l3Pro Ala194Thr + Val197Thr + Asnl98Gln + Pro204Gly + Gly205Asp

	+ Thr207Asp Ala194Asn + Gly196Pro	-8-	Erc26dhen	4	Thron7sen	-6-	Turanscue
	+ Glv213Asn	T	erocamph	,	IHLEGIASO		191200093
	Ala194Thr + Pro195Gln	+	Gln200Ser	+	Pro204Glu	*	Thr207Asp
5	+ Gly213Pro						
	Vall97Pro + Asn198Glu	*	Gln200Asp	÷	Leu211Ala	+	Asn212Ser
	+ Gly213Pro Asn198Asp + Gln200Glu	ı.	Tur203V=1	wh.	Lou211Thr	à	April 12Sar
	+ Gly213Pro		1 1 2 2 2 2 2 2 2 2 2	`	200000000000000000000000000000000000000	•	riona Laber
10	Pro195Gln + Asn198Asp	÷	Val199Gln	÷	Gln200Glu	4	Pro204Asn
	+ Ala209Pro						
	Ala194Gly + Gly196Asn	÷	Asn198Asp	4	Gln200Asp	Ť	Thr207Gly
	+ Asn212Ser Gln200Asp + Thr202Asn		Turonania	,è	Thr20361n	.2.	Lau23161u
15	+ Thr214Pro		1 y 2 2 O M 2 B	,	11112010111	•	neue raoau
	Val197Asp + Val199His	÷	Tyr203Val	+	Tyr208His	+	Leu211Asp
	+ Gly213Pro						
	Pro195Asn + Val197Gln	+	Val199Gln	÷	Thr207Asp	4	Ala209Glu
20	+ Gly213Ser Asn198Gln + Gln200Asn		muv003X1 s	.4.	Throngan	.2.	THE SHOULD
20	+ Ala209Asp	7	iyradanın	4	THEFOLYMAN		171200441
	Val197Ala + Asn198Gln	+	Pro204Ser	4	Tyr208Thr	+	Ser210Glu
	+ Asn212Glu						
	Gly196Asn + Gln200Asn	÷	Pro204Gln	+	Ser210Asp	*	Asn212Glu
25	+ Thr214Pro Pro195Gln + Val199Pro	4	Sar2308en	٠	5en21261s	a.	G1 1/21 32 en
	+ Thr214Glv		nerernuch		nonexecuto		Granomon
	Pro195Gly + Gln200Ser	÷	Thr207Pro	+	Tyr208Gln	+	Ser210Glu
	+ Asn212Glu						
30	Pro195Gly + Val199Cys	+	Thr202Asn	+	Tyr208His	÷.	Ser210Glu
	+ Asn212Asp Val199His + Thr202Gly	÷	Pro204Gin	4	A1a209Thr	+	Ser210Asp
	+ Asn212Asp		LLULUTULII	•	2020000000000		002220000
	Asn198Gln + Thr202Pro	÷	Ala209Ser	÷	Ser210Glu	+	Asn212Glu
35	+ Gly213Pro						
	Ala194Ser + Vall99Gln	4	TALSORGIA	*	SerzioAsp	÷	LeuziiGin
	+ Asn212Asp Ala194Asn + Val199Glv	+	Gly2055er	4	Ala209His	÷	Ser21061u
	+ Asn212Glu						
40	Ala194Ser + Thr202Asn	4	Pro204Gly	Ť	Tyr208Glu	÷	Ser210Glu
	+ Gly213Gln		ms000003		m	,	02101
	Pro195Gln + Val199Asn + Leu211Ile	ą.	Inrzo/Giy	1	TATEGORSD	*	parkingsb
	Pro195Gln + Gln200Asn	+	Tyr203Gln	+	Tyr208Glu	4	Serž10Glu
45	+ Asn212Gln		-				
	Ala194His + Tyr203Asn	+	Tyr208Asp	÷	Ser210Asp	-5-	Leu211His
	+ Thr214Ser Gly196Asn + Val197Gin		mk vanana	.2.	#w=20001u	4	73-2697en
	+ Ser210Glu	T	INT SOSMON		TYLEOGGAG	-4-	PLI ELZ O PROTE
50	Ala194Asn + Gln200Ser	÷	Tyr203Met	÷	Ser206Glu	÷	Tyr208Glu
	+ Leu211Val						
	Ash198Ser + Pro204Gly	4	Ser206Glu	•	Tyr208Asp	*	Asn212Gln
	+ Thr214Gly Ala194Pro + Gln200Asn	٠.	サルトラロウロテル	.2-	Tur-203Mat	.4	Aen212Aen
	WIGHTO A CHRETOTU	*	AHERUZELO	-2"	- 22 E E O O O O C C	. 5.	course cerains

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+ Thr214Asp Pro195Ser + Asn198Glu + Gln200Ser + Thr202Asn + Gly205Pro + G1v213Asp Pro195Ser + Asn198Glu + Val199Ala + Ala209Glu + Leu211Asn + Thr214Gly Pro195Glv + Asn198Glu + Gln200Asn + Thr202Pro + Tvr203Ile + Ala209Glu Vall97Ser + Asnl98Asp + Tvr203Pro + Tvr208Met + Ala209Asp + Leu211Gln Pro195Ser + Asn198Asp + Gln200Ser + Tyr208Mst + Ala209Asp + Leu211Met Gly196Asn + Vali97Asp + Vali99Gln + Gln200Glu + Gly205Asn + Gly213Pro Gln200Glu + Thr202Gln + Tyr203Met + Ala209Asn + Leu211Ala + Asn212Asp 15 Alai94Pro + Gly196Pro + Gln200Asp + Thr202Asn + Tyr208Ser + Asn212Glu Vall97Glv + Vall99Ser + Gln200Glu + Tyr203Glv + Asn212Glu + Gly213Pro Pro204Asp + Thr207Gln + Tvr208Leu + Ala209Asp + Asn212Ser 20 + Thr214Asn Alal94Ser + Pro195Gln + Thr202Ser + Pro204Asp + Ala209Asp + Thr214Asn Pro195Asn + Thr202Ser + Tvr203Leu + Tvr208Asp + Ala209His + Leu2llAsp Ala194Asn + Gly196Pro + Ser206Glu + Tyr208His + Ala209Asp + Thr214Gly Pro204Gln + Gly205Asn + Ser206Glu + Thr207Gly + Ala209Asp + Leu211Cvs Vall97Gln + Thr202Gln + Pro204Gly + Ser206Asp + Ala209Asp + Thr214Ser Ala194Gly + Val197Gln + Asn198Gln + Tyr203Val + Ser206Asp + Ala209Asp Gly196Ser + Val197Asn + Gln200Asp + Thr202Pro + Thr207Asp + Asn212Gln 35 Ala194Glv + Glv196Ser + Ser210Asp + Leu211Ser + Asn212Gln + Gly213Glu Vall97Thr + Tyr203His + Thr207Gln + Tyr208Pro + Ser210Asp + Gly213Asp Asn198Ser + Val199Cys + Tyr203Val + Gly205Ser + Ser210Asp 40 + Gly213Asp Val197His + Val199Asn + Pro204Gln + Ser210Asp + Asn212Ser + Gly213Asp Glv196Ser + Val197Ala + Gln200Asn + Thr202Pro + Ser210Glu + Gly213Glu Asn198Glu + Tyr203Gly + Gly205Gln + Thr207Pro + Tyr208Val + Thr214Glu Ala194Gly + Gly196Asn + Asn198Asp + Tyr203Leu + Tyr208His + Thr214Glu Pro195Gly + Asn198Glu + Val199Cys + Ala209Gln + Asn212Gln + Thr214Asp Asn198Asp + Vall99Asn + Thr202Asn + Pro204Gln + Asn212Gln + Thr214Asp Val199Pro + Gln200Asp + Tvr203Asn + Leu211Pro + Gly213Glu

+ Thr214Asn Pro195Ser + Glv196Pro + Vall99Ala + Gln200Asp + Asn212Gln + Glv213Asp Ala194Thr + Pro195Glv + Glv196Pro + Gln200Glu + Glv205Asn + Gly213Glu Vall99His + Gln200Glu + Pro204Ser + Leu211His + Gly213Glu + Thr214Gln Asn198Asp + Gln200Ser + Glv205Ser + Tyr208Asp + Leu211Ala + Asn212Ser Ala194Ser + Asn198Asp + Thr202Ser + Tyr208Asp + Ala209Pro + Glv213Gln Gln200Asn + Tyr203Pro + Pro204Glu + Gly205Pro + Ser210Asp + Leu211Pro Val197Ser + Tyr203Pro + Pro204Asp + Ala209Gly + Ser210Asp + Thr214Asn 15 Glv196Asn + Pro204Glu + Ser210Glu + Leu211Pro + Asn212Ser + Thr214Glv

TABLE 29

Loop 6 - Heptuple Mutation Variants 20 Pro195Ser + Asn198Ser + Val199Met + Ser206Glu + Thr207Ser + Gly213Asn + Thr214Gln Alal94Gln + Pro195Asn + Val197Ser + Thr202Ser + Tyr203Ser + Ala209Ser + Asn212Asp Val197Asp + Gln200Asn + Thr202Pro + Gly205Gln + Thr207Gly + Tvr208Met + Leu211Val Als194Ser + Pro195Glv + Asn198Ser + Thr202Pro + Ser206Glu + Tvr208Ala + Thr214Gln Ala194Pro + Pro195Asn + Thr202Glv + Tyr203Thr + Ser206Glu 30 + Leu211Ser + Thr214Pro Glv196Gln + Val197Thr + Gln200Asn + Tvr203Cvs + Glv205Ser + Ser210Glu + Leu211Val Alal94His + Val199Ser + Thr202Gly + Thr207Asn + Leu211Met + Gly213Glu + Thr214Pro Vall99Gly + Tvr203Cys + Pro204Gly + Thr207Asn + Ala209His + Asn212Asp + Gly213Asn Ala19461n + Gly196Pro + Tyr203Ser + Pro204Ser + Tyr208Ser + Leu211Glu + Thr214Pro Gly196Gln + Gly205Asn + Thr207Asp + Tyr208Met + Asn212Gln 40 + Glv213Ser + Thr214Pro Gly196Gln + Val199Cys + Ser206Glu + Thr207Pro + Ala209Pro + Leu21111e + Gly213Ser Thr202Pro + Tyr203Val + Pro204Asn + Ser206Asp + Asn212Ser + Gly213Ser + Thr214Gly Alai94Thr + Pro195Asn + Gly196Pro + Gln200Asn + Pro204Ser + Asn212Glu + Gly213Gln Asn198Gln + Gln200Ser + Pro204Gln + Gly205Asn + Thr207Glu + Asn212Ser + Glv213Ser Ala194Ser + Gly196Ser + Asn198Ser + Tyr203Gly + Gly205Pro + Ser206Glu + Glv213Pro Ala194Thr + Glyl96Gin + Val197Pro + Thr202Gln + Pro204Ser + Ala209Gly + Asn212Glu

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Pro195Gin + Gly196Pro + Asn198Gin + Pro204Ser + Gly205Giu + Tyr208Gln + Gly213Asn Vall99Thr + Tyr203Gln + Pro204Gln + Gly205Asn + Thr207Glu + Leu211Thr + Thr214Gln Vall97Thr + Asn198Glu + Thr202Gly + Gly205Pro + Thr207Pro ŝ + Tyr208Met + Gly213Gln Pro195Glv + Glv196Ser + Thr202Glv + Tvr203Gln + Pro204Gln + Tvr208Pro + Thr214Gln Pro195Asn + Asn198Asp + Gln200Ser + Pro204Gly + Gly205Gln + Tyr208Glv + Ala209Asn 10 Pro195Asn + Vall99His + Pro204Asn + Ala209Pro + Leu211Thr + Asn212Ser + Thr214Pro Asn198Gln + Val199Thr + Gln200Asp + Pro204Asn + Leu211Val + Asn212Ser + Gly213Gln Pro195Ser + Glv196Ser + Val197Met + Val199Glv + Glv205Pro + Ser210Glu + Asn212Gln Alal94Thr + Pro195Gln + Asn198Gln + Thr202Asn + Thr207Asp + Tyr208Thr + Gly213Ser Pro195Gln + Glv196Asn + Glv205Glu + Thr207Pro + Tyr208Asn + Ala209His + Asn212Ser 20 Asn198Gln + Thr202Pro + Thr207Pro + Leu211Pro + Asn212Glu + Gly213Asn + Thr214Ser Alai94Pro + Vali97Met + Pro204Ser + Thr207Gln + Tyr208Asn + Ala209Gln + Thr214Glv Ala194Asn + Val197Cys + Pro204Asn + Tyr208Thr + Ala209Pro + Ser210Glu + Leu211Ser Gly196Asn + Val197Gly + Tyr203Pro + Gly205Asp + Leu211Ala + Gly213Asn + Thr214Ser Ala194Thr + Pro195Asn + Tyr203Pro + Gly205Ser + Ser210Glu 30 + Leu2llAla + Glv213Pro Ala194His + Gly196Asn + Val197Met + Asn198Ser + Ser206Asp + Leu2llAsn + Asn212Ser Alai94Thr + Gly196Ser + Val199Ser + Thr202Asn + Ala209Pro + Leu211Pro + Gly213Gln Gly196Gln + Vall99His + Thr202Pro + Tyr203Thr + Pro204Asp + Glv205Ser + Ala209Asn Valigacys + Valigagly + Thr202Gln + Tyr203His + Gly205Glu + Tvr2081le + Thr214Gln Ala194Glv + Val197Cys + Asn198Asp + Gln200Ser + Tyr203Leu 40 + Ala209Gln + Asn212Gln Alai94Gly + Tyr203Cys + Gly205Gln + Ser206Glu + Tyr208Met + Leu211Cys + Thr214Gly Gly196Ser + Val199Gln + Thr202Ser + Tyr203His + Pro204Gln + Tyr208Leu + Glv213Pro Asn198Gln + Thr202Asn + Tyr203Ala + Pro204Glu + Tyr208Gly + Ala209Gln + Thr214Gln Ala194Asn + Pro195Gln + Pro204Gly + Ser206Glu + Thr207Ser + Tyr208Ala + Asn212Ser Ala194Pro + Pro195Gln + Val197Ser + Asn198Ser + Gln200Glu + Thr202Ser + Glv205Ser Pro195Ser + Glv196Ser + Val199Glv + Thr202Glv + Pro204Glu + Leu211Ala + Thr214Asn Ala194Thr + Gly196Pro + Asn198Ser + Pro204Asn + Tyr208Gly + Ser210Asp + Thr214Asn

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Alal94Pro + Val199Asn + Thr202Gln + Pro204Gln + Glv205Asp + Thr207Ser + Ala209Pro Ala194Pro + Pro195Glv + Vall97Cvs + Vall99Gln + Tvr203Cvs + Tyr208His + Gly213Glu Val197Asp + Val199Ser + Gly205Pro + Thr207Gly + Leu211Thr + Asn212Gln + Glv213Ser Alal94Pro + Pro195Ser + Gln200Asn + Thr202Pro + Tyr208His + Glv213Asp + Thr214Gly Ala194Thr + Val197Asn + Val199Pro + Gln200Asp + Thr202Ser 10 + Thr207Asn + Tyr208Leu Pro195Ser + Gly196Gln + Vall97Ala + Thr202Gln + Tyr203Gly + Tvr208Cvs + Glv213Asn Ala194Gln + Val199Gln + Thr202Glv + Pro204Asn + Glv205Glu + Ala209His + Leu211His Pro195Asn + Vall99Thr + Tyr203Gly + Gly205Gln + Ser206Asp 15 + Asn212Ser + Glv213Pro Ala194Gln + Pro195Ser + Gly196Gln + Thr202Gln + Ala209His + Asn212Ser + Thr214Glu Gly196Pro + Val197Cys + Tyr203Pro + Gly205Ser + Ser206Asp 20 + Leu211Ile + Thr214Glv Glv196Asn + Val197Glv + Val199His + Thr202Ser + Ala209His + Asn212Glu + Thr214Gln Glyl96Gin + Gin200Ser + Thr202Gin + Gly205Gin + Ala209Ser + Gly213Asp + Thr214Glu Vall99Gly + Gln200Asn + Thr202Gln + Gly205Ser + Ala209Glu + Ser210Asp + Leu211Asn Val199Pro + Gln200Asn + Tvr203Val + Ala209Asp + Ser210Asp + Leu2llSer + Glv213Pro Ala194Glv + Tvr203Val + Gly205Asn + Thr207Gly + Ala209Glu 30 + Ser210Asp + Leu211Pro Pro195Gln + Thr202Gly + Tyr203Val + Ala209Glu + Ser210Glu + Gly213Ser + Thr214Gln Pro195Asn + Vall97Ser + Tyr208Thr + Ala209Glu + Ser210Asp + Asn212Ser + Thr214Gln 35 Alal94Asn + Glv196Ser + Val199Glv + Thr202Pro + Tyr203Leu + Asn212Glu + Gly213Asp Val197Cys + Asn198Ser + Gln200Ser + Thr202Asn + Thr207Gln + Asn212Asp + Gly213Asp Gly196Pro + Thr202Asn + Pro204Asp + Gly205Glu + Ala209His + Leu211His + Gly213Ser 40 Pro195Gly + Gly196Gln + Tyr203Thr + Thr207Asn + Ser210Asp + Lou211Asp + Asn212Ser Ala194Gly + Gly196Pro + Thr202Gln + Tyr203Val + Gly205Ser + Ser210Asp + Leu211Asp Alal94His + Vall99Cys + Tyr203Ala + Tyr208Gly + Ser210Asp 45 + Leu2l1Asp + Gly213Pro Ala194His + Gly196Ser + Val197Cys + Val199Ser + Gly205Glu + Ser206Glu + Tvr208Ser Ala194His + Gly196Ser + Val197Thr + Val199Cys + Gly205Asp + Ser206Glu + Thr214Gln 50 Thr202Asn + Tyr203Thr + Gly205Glu + Ser206Asp + Ala209Gln + Leu211Thr + Thr214Gly Ala194Pro + Val197Met + Asn198Ser + Val199Asn + Thr202Ser + Ser206Asp + Thr207Glu

Pro195Asn + Val199Met + Thr202Gly + Ser206Glu + Thr207Asp + Tvr208Thr + Asn212Ser Pro195Glv + Glv196Asn + Vall99Gln + Tvr203His + Ser206Glu + Thr207Asp + Asn212Gln Pro195Asn + Val199Ala + Glv205Pro + Ser206Glu + Thr207Asp + Tyr208Gly + Asn212Ser Pro195Asn + Gly196Ser + Vall97Ala + Pro204Ser + Ser206Glu + Thr207Asp + Asn212Gln Pro195Asn + Val197Thr + Ser206Asp + Thr207Asp + Leu211Thr + Glv213Ser + Thr214Ser 10 Ala194Thr + Val197Cys + Asn198Ser + Thr207Asp + Tyr208Asp + Asn212Ser + Gly213Asn Ala194Thr + Gln200Asp + Thr202Gln + Ala209His + Ser210Asp + Leu211Glv + Thr214Glv 15 Pro195Gln + Gln200Asp + Tvr203Ala + Glv205Asn + Tvr208Ser + Ser210Asp + Gly213Asn Alal94Thr + Val199Pro + Gln200Glu + Thr207Gly + Ser210Glu + Leu211Ser + Gly213Asn Vall97Ser + Gln200Glu + Tyr203Leu + Pro204Asn + Ala209Gly + Ser210Asp + Leu211Asn 20 Gly196Gln + Asn198Gln + Val199Pro + Gln200Asp + Thr202Gly + Pro204Glv + Ser210Asp Asn198Gln + Val199Cys + Gln200Glu + Glv205Gln + Ser210Asp + Glv213Ser + Thr214Gly Asn198Gln + Gln200Glu + Gly205Fro + Thr207Ser + Ala209Asn + Ser210Glu + Thr214Asn Gln200Glu + Thr202Asn + Thr207Ser + Tyr208Pro + Ser210Glu + Gly213Gln + Thr214Gly Alal94Pro + Pro195Ser + Gly196Asn + Val197Asp + Val199Thr 30 + Pro204Gly + Asn212Glu Gly196Asn + Asn198Glu + Tvr203Glv + Pro204Gln + Ser210Asp + Leu211Val + Asn212Ser Glv196Pro + Val197Glv + Asn198Aso + Thr202Pro + Tvr203Val + Thr207Asn + Ser210Glu 35 Pro195Asn + Gly196Pro + Asn198Asp + Thr202Ser + Pro204Gln + Ser210Asp + Gly213Gln Pro195Ser + Val197Pro + Asn198Glu + Val199Met + Thr207Ser + Ser210Asp + Thr214Gln Ala194Ser + Gly196Asn + Val197Met + Asn198Asp + Val199Thr 40 + Tvr208Met + Leu211Glu Asn198Asp + Val199Gln + Pro204Ser + Leu211Asp + Asn212Ser + Gly213Pro + Thr214Asn Pro195Gln + Asn198Asp + Thr202Pro + Gly205Gln + Tyr208Met + Leu211Glu + Glv213Asn Gly196Pro + Gln200Asp + Thr202Ser + Tyr203Thr + Tyr208His 45 + Ala209Glu + Leu211Ile Ala194Thr + Gln200Asn + Thr202Pro + Pro204Asp + Ser206Glu + Thr207Asn + Ala209Ser Gly196Pro + Pro204Asp + Gly205Ser + Ser206Asp + Tyr208Gly 50 + Gly213Gln + Thr214Gly Pro195Gln + Val197Gln + Gin200Ser + Pro204Glu + Ser206Asp + Ala209Gly + Thr214Gln Alal94Thr + Pro195Gly + Vall97Pro + Pro204Asp + Ser206Glu + Leu211Val + Gly213Ser

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Pro195Asn + Gly196Ser + Pro204Glu + Ser206Asp + Thr207Gly + Tvr208Val + Ala209Thr Prol95Asn + Glv196Prc + Val197Gln + Asn198Asp + Tyr203Gln + Tyr208Asn + Asn212Asp Gly196Gln + Val197Thr + Asn198Asp + Val199Gly + Thr202Fro + Tyr208Asn + Asn212Glu Pro195Asn + Asn198Asp + Vall99Asn + Thr202Gln + Ala209Pro + Asn212Asp + Glv213Gln Alal94Glv + Val197Met + Asn198Asp + Gin200Glu + Thr202Asn + Pro204Asn + Tvr208Asn 10 Pro195Ser + Val197Gln + Asn198Glu + Val199Cvs + Gin200Asp + Glv205Ser + Ala209Pro Pro195Gln + Gly196Pro + Asn198Glu + Val199Ser + Gln200Asp + Gly205Ser + Thr214Asn 15 Alal94Gln + Pro1955er + Asn198Glu + Gln200Asp + Thr207Gln + Tyr208Leu + Asn212Gln Ala194Pro + Pro195Asn + Gln200Glu + Pro204Gln + Thr207Gln + Tyr208Asp + Gly213Gln Vall99Thr + Gln200Asp + Tyr208Glu + Ala209Thr + Leu211Ser + Asn212Ser + Gly213Asn Glv196Pro + Val197Glu + Asn198Gln + Val199Met + Tvr208Met + Glv213Asp + Thr214Asn Pro195Glv + Val197Glu + Val199Thr + Gln200Ser + Glv205Asn + Ala209Glv + Leu211Glu Val197Met + Val199Cvs + Glv205Pro + Tvr208Ile + Leu211Asp + Asn212Ser + Gly213Asp Pro195Gln + Asn198Ser + Val199Gln + Pro204Ser + Ser210Asp + Leu211Cvs + Asn212Glu Pro195Ser + Gly196Pro + Asn198Gln + Pro204Gln + Ala209Thr 30 + Ser210Glu + Asn212Glu Ala194Gly + Asn198Gln + Val199Gln + Thr207Ser + Ser210Asp + Leu211Gly + Asn212Asp Ala194Gln + Val197Gly + Thr202Ser + Pro204Ser + Ser210Glu + Asn212Glu + Glv213Ser 3.5 Ala194Asn + Asn198Ser + Thr202Pro + Ser210Glu + Leu211Cys + Asn212Asp + Gly213Ser Pro195Gly + Vall97Thr + Thr202Asn + Gly205Ser + Ser210Asp + Asn212Glu + Glv213Ser Pro195Gln + Gly205Gln + Ala209Gln + Ser210Asp + Leu211Asn + Asn212Glu + Thr214Gln 40 Val199His + Pro204Asn + Tyr208Ile + Ala209Thr + Ser210Glu + Leu211Gln + Asn212Asp Vall97Asn + Asn198Gln + Tyr203Pro + Pro204Asn + Ser210Glu + Asn212Glu + Thr214Gln Ala194Pro + Gly196Ser + Gln200Ser + Gly205Gln + Tyr208Gly + Ser210Glu + Asn212Glu Pro195Ser + Val197Gly + Asn198Gln + Val199Gln + Gln200Ser + Ser210Glu + Asn212Asp Asni98Gln + Gln200Asn + Thr207Glv + Tvr208Glu + Ser210Glu + Asn212Ser + Thr214Asn Pro195Gly + Thr202Ser + Tyr208Glu + Ala209Asn + Ser210Glu + Asn212Gln + Thr214Asn Vall99Thr + Thr202Ser + Gly205Pro + Ser206Glu + Tyr208Glu + Leu211His + Asn212Ser

Ala194Gln + Gly196Pro + Asn198Gln + Tyr203lle + Ser206Asp + Tyr208Asp + Gly213Gln Ala194Ser + Pro195Ser + Thr202Ser + Glv205Gln + Ser206Asp + Tvr208Asp + Asn212Gln Pro195Gly + Val197His + Tyr203Gln + Thr207Pro + Asn212Asp 5 + Glv213Ser + Thr214Asp Pro195Gly + Vall97Met + Thr202Asn + Tyr208Met + Leu211Thr + Asn212Glu + Thr214Asp Val197Ser + Asn198Gln + Thr202Ser + Pro204Glu + Thr207Ser + Tyr208Asp + Ala209Ser Alal94Pro + Val199Asn + Pro204Asn + Tyr208Glu + Leu211Gly + Asn212Gln + Gly213Ser Pro195Gln + Val197Glu + Val199Gly + Gln200Ser + Thr207Ser + Ser210Glu + Leu211Asn Pro195Ser + Val197Asp + Val199Cys + Pro204Gly + Tyr208Ser 15 + Ser210Glu + Asn212Ser Ala194Gln + Val197Asp + Asn198Ser + Thr202Asn + Thr207Asp + Ser210Glu + Leu211His Val197Asp + Gln200Asn + Tyr203Thr + Tyr208Val + Ser210Asp + Asn212Ser + Thr214Ser Ala194Pro + Val197Asp + Gln200Ser + Thr202Gly + Leu211Cys + Gly213Asn + Thr214Glu Pro195Ser + Val197Glu + Asn198Gln + Tyr208Ile + Ala209His + Leu211Val + Thr214Glu 25 Pro195Gly + Val197Asp + Gln200Ser + Thr202Pro + Ala209Thr + Gly213Gln + Thr214Asp Pro195Asn + Gly196Pro + Asn198Asp + Pro204Asn + Gly205Asn + Ala209Asn + Gly213Asp Alsi94Pro + Asn198Asp + Val199Gln + Gln200Ser + Thr207Pro + Ala209Asp + Gly213Asn 30 Val197Asp + Val199His + Gln200Glu + Thr202Pro + Tyr203Ile + Thr207Glv + Thr214Glv Vall97Glu + Gln200Asp + Tyr203Ile + Pro204Gln + Ala209Gly + Leu211Ile + Thr214Pro Pro195Asn + Gly196Ser + Val199Met + Gln200Asp + Tyr203Ala 35 + Asn212Asp + Gly213Asn Ala194Thr + Gly196Gln + Gln200Glu + Tyr203Val + Tyr208Ala + Leu211Ala + Asn212Glu Val197Asn + Asn198Gln + Pro204Asp + Tyr208Mst + Ala209Glu 40 + Asn212Ser + Gly213Asn Pro195Asn + Thr202Gly + Tyr203Asn + Pro204Glu + Gly205Asn + Thr207Ser + Ala209Glu Ala194Pro + Gly196Pro + Tyr203Ala + Thr207Gln + Leu211Glu + Gly213Pro + Thr214Glu Asn198Gln + Val199Thr + Thr202Pro + Pro204Gln + Ala209Thr 45 + Leu211Glu + Thr214Asp Ala194His + Val199Cys + Gln200Glu + Tyr203Ile + Gly205Asn + Thr207Glu + Tyr208Met Vall99Pro + Gln200Asp + Pro204Gln + Gly205Asn + Thr207Asp + Tyr208Cys + Thr214Pro 50 Ala194His + Pro195Gln + Glv196Gln + Vall99His + Gln200Glu + Thr207Glu + Asn212Ser Alai94Gly + Asn198Gln + Gln200Asn + Tyr203Let + Ser210Asp + Leu211Gly + Gly213Glu

	Asn198Gln + Gln200Asn + Thr202Ser + Gly213Glu + Thr214Asn	4	Ser210Asp	+	Leu211Ser
	Pro195Asn + Vall97Met + Tyr203Gly	4	Gly205Pro	÷	Tyr208His
5	+ Ser210Asp + Gly213Asp Pro195Ser + Gln200Asn + Thr207Fro		002210010		7 mm 2 7 2 Mm+
3	+ Gly213Glu + Thr214Gln	A.	Setsionia	Ť	redrituer
	Vall97Gln + Vall99Ser + Thr202Asn	4	Tvr208Glv	÷	Ala209G1v
	+ Ser210Glu + Gly213Asp		0,10000		***************************************
	Gln200Asn + Pro204Gln + Thr207Glu	-	Ala209Ser	÷.	Ser210Asp
10	+ Leu211Thr + Gly213Asn				
	Ala194Gln + Thr202Gly + Tyr203Asn	÷	Thr207Asp	4	Ser210Asp
	+ Leu211Cys + Gly213Pro				
	Pro195Gln + Val199Gln + Gly205Gln	+	Thr20/Glu	+	Tyrzosite
15	+ Ser210Asp + Thr214Gly Pro195Gly + Val197His + Val199Met		Turanamer		20x26761v
13	+ Ser210Asp + Asn212Gln	*	1312021111	4	11112010111
	Ala194Gln + Pro195Gln + Asn198Ser	+	Val199Gln	4	Pro204Gln
	+ Thr207Glu + Ser210Glu				
	Vall97Pro + Asn198Glu + Vall99Thr	+	Pro204Asn	÷	Leu211Cys
20	+ Asn212Ser + Thr214Asp				
	Ala194Ser + Val199Thr + Gln200Glu	+	Tyr203Cys	+	Tyr208Gly
	+ Leu211Gly + Gly213Glu				
	Val199Pro + Gln200Asp + Tyr203Asn	+	Pro204Gly	+	LeuZllPro
25	+ Gly213Glu + Thr214Asn Ala194Gln + Asn198Glu + Thr207Ser		#W-2007 Da	. 2.	Baw 23 203 m
23	+ Gly213Gln + Thr214Gln	*	171200010	T	MOUZIZOIN
	Pro195Gln + Asn198Asp + Gln200Ser	÷	G1v205Ser	ą.	Tyr208Asp
	+ Leu2llAla + Asn2l2Ser				
	Gly196Pro + Val197Asp + Asn198Gln	÷	Val199Ala	4	Pro204Gln
30	+ Ala209Asp + Gly213Asn				
	Pro195Ser + Asn198Gln + Val199Gly	4	Pro204Glu	÷	Ala209Gly
	+ Ser210Asp + Asn212Gln		m)		* > - 0 0 0 0 1
	Pro195Ser + Gln200Ser + Pro204Glu + Ser210Asp + Asn212Gln	4.	INEZUTEEO	d,	MISSORPH
35	Ala194His + Gly196Ser + Val197Gly	4	Valiagaen	+	G15200G1u
	+ Pro204Glu + Ala209Thr		10222771000		WW.112.70 W.A.
	Gly196Pro + Asn198Ser + Pro204Asn	4	Tyr208Gly	÷	Ala209Asp
	+ Leu211Thr + Gly213Asp				
	Gly196Pro + Vall99Thr + Gln200Asp	÷	Thr202Asn	÷	Tyr203Asn
40	+ Ser206Glu + Ala209Ser		01 . 0C00Y		n 20 int
	Pro195Ser + Gly196Pro + Vall99Pro + Ser206Aso + Leu2l1Ala	Ť	GIUXOOGIU	7	LIOS04GIII
	Pro195Ser + Gln200Asp + Thr202Gln	.2.	Pro20461n	4	Ser2066111
	+ Tyr208Gly + Ala209Gly			•	
45	Gly196Asn + Val199Ser + Gln200Glu	÷	Thr202Pro	4	Ala209Thr
	+ Leu211Cvs + Thr214Asp				
	Vall97Asn + Gln200Glu + Tyr203Gln	4.	Gly205Pro	+	Ala209Thr
	+ Leu211Val + Thr214Glu				
	Pro195Gly + Tyr203Gly + Ser206Glu	4	TyrzusGiy	+	Alazo9GIn
50	+ Ser210Glu + Leu21111e Gly196Asn + Val197His + Val199Ala		Dv0204800	4	Saransann
	+ Ser210Asp + Leu211Thr	r	E COL VAMOII	r	ners comet
	Ala194Gln + Val197Ser + Val199Pro	4	Ser206Asp	+	Ser210Glu
	+ Leu2l1Pro + Thr214Gly				

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Alal94His + Gln200Ser + Thr202Asn + Ser206Glu + Tyr208Cys + Ser210Asp + Asn212Ser Vall97Thr + Thr202Ser + Pro204Gly + Gly205Asn + Ser206Asp

74

+ Ser210Glu + Leu211Pro

5

TABLE 30

Loop 6 - Octuple Mutation Variants Pro195Ser + Val197Ser + Asn198Ser + Val199Gly + Tyr203Thr + Thr207Asn + Tvr208Met + Asn212Glu Pro195Gln + Gly196Gln + Val199Gln + Tyr203Gln + Tyr208Met + Ala209Gly + Leu211Val + Gly213Asp Pro195Gln + Asn198Gln + Vall99His + Pro204Gly + Ser206Glu + Thr207Gln + Tvr208Ser + Leu211Gln Alai94Thr + Val197Met + Val199His + Thr202Ser + Tvr203Ile 15 + Thr207Gln + Tvr208Pro + Leu211Gly Pro195Gln + Val197Asn + Val199Cys + Tyr203Met + Pro204Asn + Gly205Glu + Thr207Pro + Tyr208Ser Gly196Ser + Gln200Asn + Pro204Asp + Gly205Ser + Thr207Pro + Tyr208Met + Gly213Gln + Thr214Ser Val197Gln + Gln200Asn + Tyr203His + Pro204Asp + Gly205Ser + Tyr208Thr + Ala209Gln + Leu211Pro Pro195Glv + Glv196Ser + Vall97Pro + Vall99Ser + Thr202Asn + Ala209Glu + Leu211Ser + Glv213Pro Ala194His + Gly196Ser + Val197Asn + Asn198Ser + Tyr203Leu 25 + Pro204Asn + Thr207Ser + Ala209Thr Alai94Pro + Glv196Pro + Val199Met + Gln200Asp + Thr202Asn + Thr207Asn + Ala209Pro + Glv213Pro Pro195Asn + Gly196Pro + Vall99Thr + Thr202Gln + Thr207Gly + Tyr208Ser + Ser210Asp + Asn212Ser Ala194Thr + Pro195Asn + Gly196Gln + Thr202Pro + Pro204Ser + Gly205Pro + Tyr208Gln + Leu211Asp Alal94Glv + Pro195Ser + Val197Ala + Thr202Glv + Tvr203Glv + Pro204Gln + Glv205Ser + Leu211Glu Pro195Asn + Val197Glu + Val199Thr + Gln200Asn + Thr202Pro 35 + Tyr203Ile + Pro204Ser + Leu211Cys Ala194His + Pro195Gln + Val199Cys + Gln200Asp + Tyr203Ala + Thr207Ser + Glv213Gln + Thr214Pro Ala194Gln + Gly196Gln + Val199His + Thr202Pro + Tyr203Thr + Pro204Asp + Gly205Ser + Ala209Asn Pro195Ser + Gly196Ser + Gln200Asn + Tyr203His + Thr207Pro + Leu211Met + Gly213Glu + Thr214Gln Vall97Cvs + Asn198Ser + Vall99Ala + Gln200Asp + Tvr203His + Leu211Asn + Asn212Gln + Glv213Asn Ala194Gln + Glv196Pro + Asn198Gln + Val199His + Tvr203Val 45 + Thr207Ser + Ala209Ser + Leu211Asn Pro195Glv + Glv195Ser + Val197Pro + Thr207Glv + Leu211Thr + Asn212Ser + Gly213Asn + Thr214Glu Vall97Asn + Thr202Gly + Tyr203Ala + Gly205Gln + Tyr208Ile + Ala209Thr + Ser210Asp + Leu211Gly 50 Ala194Asn + Asn198Gin + Val199Ser + Thr202Gly + Tyr203Ile + Ala209Thr + Ser210Asp + Thr214Ser Pro195Ser + Glyl96Asn + Vall97Asn + Asn198Ser + Thr202Asn

+ Tyr203Cys + Tyr208Asn + Leu211Thr Ala194Gly + Pro195Ser + Gly196Gln + Val199Ala + Thr202Pro + Thr2075er + Asn212Ser + Thr214Asp Val197Cvs + Val199Pro + Thr202Pro + Tvr203Ser + Ser206Glu + Thr207Gln + Ala209Glv + Thr214Glv Alal94Glv + Pro195Gln + Glv196Gln + Asn198Ser + Val199Met + Thr202Pro + Thr207Glu + Thr214Gly Ala194His + Pro195Gln + Val197Gln + Asn198Gln + Tvr203Ser + Ser206Glu + Tvr208Ala + Leu211Ala Ala194Glv + Glv196Ser + Tvr203His + Pro204Asn + Ser206Asp + Tvr2081le + Leu211Gln + Asn212Ser Gly196Pro + Gln200Ser + Tyr203Gln + Pro204Ser + Gly205Ser + Tyr208Cys + Leu211Met + Gly213Gin Ala194Asn + Tyr203Asn + Gly205Glu + Thr207Gln + Ala209Thr 15 + Leu211His + Gly213Pro + Thr214Gln Ala194Ser + Pro195Asn + Glv196Asn + Val199Ser + Pro204Ser + Gly205Asn + Ala209Asp + Thr214Gln Pro195Asn + Gly196Gln + Thr202Pro + Gly205Ser + Ser206Glu + Tyr208Ser + Ala209Pro + Gly213Gln Alal94Thr + Pro195Glv + Val197Asp + Asn198Gln + Gly205Ser 20 + Tyr208Val + Asn212Gln + Gly213Ser Pro195Glv + Asn198Ser + Tvr203Thr + Pro204Asn + Tvr208Pro + Ala209Thr + Asn212Ser + Glv213Ser Ala194Thr + Pro1955er + Gly196Asn + Val197Met + Gln200Ser 25 + Thr202Asn + Tyr203His + Tyr208Gln Ala194His + Asn198Ser + Tyr203Gln + Pro204Gln + Ala209Pro + Leu211Asp + Asn212Glu + Gly213Asn Ala194Asn + Pro195Ser + Val197Glv + Pro204Glv + Glv205Asn + Ala209Asp + Ser210Asp + Thr214Gln Glv196Gln + Val197Pro + Gln200Asn + Thr202Asn + Glv205Gln + Ala209Glu + Ser210Asp + Thr214Pro Val197Ser + Val199Ala + Thr202Ser + Tyr203Pro + Gly205Asn + Tyr208Ile + Ala209Asp + Ser210Glu Asn198Ser + Val199Met + Gln200Ser + Pro204Ser + Tyr208Ala + Ala209Glu + Ser210Asp + Leu211Glv 35 Ala194Glv + Val197Asn + Asn198Ser + Gln200Ser + Tvr203Thr + Ala209Asp + Ser210Asp + Thr214Pro Ala194His + Pro195Ser + Asn198Ser + Tyr203Cys + Thr207Ser + Ala209Asp + Ser210Glu + Gly213Ser Pro195Ser + Vall99Asn + Gln200Ser + Pro2045er + Thr207Gly 40 + Ala209Asp + Ser210Asp + Asn212Ser Alai94Gln + Glv196Pro + Vall97Aso + Asn198Glu + Vall99Ser + G1v205Gln + Ala209Glv + Asn212Ser Pro195Gln + Val197Asp + Asn198Glu + Val199Ala + Gln200Ser + Thr202Ser + Thr207Gly + Tyr208Ala 45 Pro195Ser + Gly196Pro + Gln200Asn + Thr202Asn + Tyr203Mst + Thr207Gly + Asn212Asp + Gly213Asp Gly196Asn + Thr202Pro + Pro204Gly + Thr207Pro + Leu211Cys + Asn212Glu + Glv213Glu + Thr214Pro Glv196Asn + Asn198Gln + Gln200Ser + Thr202Pro + Tyr203Cys + Pro204Asn + Asn212Asp + Glv213Glu Asn198Ser + Val199Gly + Tyr203Ala + Pro204Asp + Gly205Glu + Tyr208Met + Ala209Ser + Leu211Pro Vall97Cys + Vall99Asm + Thr202Gln + Pro204Asp + Gly205Asp

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+ Ala209Gln + Leu211Gln + Asn212Ser
    Pro195Asn + Vall99Thr + Thr202Gly + Ala209His + Ser210Glu
      + Leu2llAsp + Asp2l2Ser + Glv2l3Asp
    Glv196Asn + Val199His + Tvr203Ala + Glv205Asp + Ser206Asp
      + Thr207Gln + Tyr208Gln + Leu211Asn
   Ala194Glv + Glv196Gln + Val199Gln + Gln200Asn + Pro204Glv
      + Gly205Asp + Ser206Asp + Thr214Ser
   Ala194Gln + Pro195Asn + Val197Ala + Gln200Asn + Tvr203Ser
      + Glv205Asp + Ser206Asp + Tvr208Ala
   Ala194Gln + Val197Gln + Pro204Asn + Gly205Asp + Ser206Glu
      + Tvr208Ala + Ala209His + Gly213Asn
    Prol95Ser + Gly196Asn + Val197Thr + Gln200Asn + Pro204Ser
      + Gly205Glu + Ser206Glu + Tyr208Gly
   Vall97Gly + Asn198Gln + Vall99Met + Gln200Asn + Tyr203His
      + Ser206Asp + Thr207Glu + Thr214Pro
15
    Ala194Gln + Pro195Glv + Glv196Pro + Thr202Pro + Ser206Asp
      + Thr207Asp + Tyr208Val + Ala209His
   Alal94Thr + Pro195Ser + Val197Gln + Asn198Gln + Thr202Ser
      + Pro204Asn + Ser206Glu + Thr207Asp
   Ala194Gln + Val199Met + Thr202Ser + Tvr203Glv + Glv205Gln
      + Ser206Asp + Thr207Glu + Glv213Ser
   Alai94Glv + Pro195Asn + Gly196Gln + Tyr203Ala + Ser206Asp
      + Thr207Glu + Ala209Thr + Asn212Gln
    Gly196Ser + Gln200Ser + Tyr203Leu + Pro204Ser + Ser206Glu
25
      + Thr207Glu + Ala209Ser + Gly213Ser
   Ala194Ser + Pro195Asn + Thr202Gln + Ser206Glu + Thr207Glu
      + Tyr208Gly + Asn212Ser + Thr214Gly
    Alal94His + Pro195Gln + Val197Als + Thr202Asn + Tyr203Pro
      + Gly205Pro + Tyr208Asp + Ala209Asp
    Ala194Gln + Pro195Gln + Val197Asn + Gln200Asp + Ala209Glv
      + Ser210Glu + Leu211Ala + Thr214Asn
    Ala194Pro + Val199Met + Gln200Glu + Thr202Glv + Pro204Gln
      + Glv205Asn + Tyr208Gln + Ser210Asp
    Gly196Pro + Val197Cys + Val199Asn + Gln200Glu + Gly205Pro
      + Tyr208Val + Ser210Glu + Thr214Pro
35
    Ala194Thr + Pro195Gly + Gly196Gln + Val197Asp + Val199His
      + Gln200Ser + Thr202Ser + Asn212Asp
    Asni98Asp + Vall99Pro + Glv205Asn + Thr207Glv + Tyr208Pro
      + Ser210Asp + Leu211Gly + Gly213Gln
   Alai94Gln + Glyl96Pro + Asni98Glu + Tyr203Gln + Thr207Gln
      + Tyr208Pro + Ala209Pro + Ser210Glu
    Ala194Pro + Asn198Asp + Val199His + Gly205Asn + Ser210Glu
      + Leu211Asn + Asn212Ser + Thr214Pro
    Asn198Glu + Val199Pro + Tvr203Asn + Thr207Pro + Ala209Asn
      + Ser210Glu + Asn212Ser + Gly213Gln
49
    Alai94Glv + Pro195Asn + Asnl98Asp + Tyr203Ala + Gly205Gln
      + Thr207Ser + Ser210Glu + Leu211Val
    Alai94Thr + Asni98Asp + Thr202Gly + Pro204Ser + Gly205Ser
      + Thr207Asn + Ala209Pro + Ser210Glu
    Alai94Gln + Asni98Asp + Tyr203Ala + Thr207Gln + Tyr208Pro
      + Ser210Glu + Leu211Pro + Asn212Ser
    Ala194Thr + Pro195Ser + Asn198Asp + Tvr203Cvs + Pro204Asn
      + Thr207Gln + Tyr208Gln + Ser210Glu
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Pro195Ser + Asn198Asp + Vall99Ser + Gln200Ser + Pro204Ser

+ Ser210Glu + Leu211Glv + Asn212Ser Ala194Gln + Pro195Ser + Gly196Pro + Gln200Glu + Pro204Asn + Gly205Pro + Ala209Glu + Leu211Cys Vall99His + Gln200Ser + Pro204Asp + Gly205Ser + Ser206Asp + Tyr208Gly + Gly213Gln + Thr214Gly Gly196Asn + Asn198Ser + Thr202Ser + Pro204Asp + Gly205Ser + Ser206Asp + Thr207Ser + Tyr208Val Val197Ala + Gln200Asn + Pro204Glu + Glv205Ser + Ser206Glu + Tyr208Val + Leu211Ser + Asn212Ser Pro195Asn + Val197Thr + Thr202Ser + Tvr203Ile + Pro204Asp 10 + Ser206Asp + Thr207Gln + Ala209Gln Pro195Glv + Val197Asn + Val199Ser + Gln200Asn + Tyr203Asn + Pro204Glu + Ser206Glu + Leu211Met Gly196Ser + Asn198Ser + Val199Met + Gln200Asn + Pro204Glu + Ser206Asp + Leu211Val + Thr214Gln 15 Alal94Gln + Gly196Asn + Asn198Asp + Gln200Ser + Thr202Asn + Pro204Asn + Asn212Glu + Thr214Asn Pro195Gly + Asn198Glu + Val199Asn + Gln2005er + Thr202Gly + Thr207Asn + Ala209Thr + Asn212Asp 20 Pro195Asn + Gly196Ser + Asn198Glu + Thr207Ser + Tyr208Ser + Ala209Pro + Asn212Asp + Thr214Asn Alal94Pro + Val197Ser + Asn198Glu + Gln200Asn + Tyr203Cys + Thr207Pro + Tyr208Thr + Asn212Asp Pro195Glv + Glv196Ser + Thr202Asn + Pro204Asn + Glv205Glu 25 + Thr207Asp + Tyr208Thr + Asn212Ser Val197Gln + Val199Asn + Thr202Pro + Glv205Glu + Thr207Glu + Tyr208Ala + Leu211Ser + Gly213Asn Ala194Ser + Pro195Ser + Vall97Gly + Pro204Asp + Gly205Ser + Thr207Glu + Tyr208Val + Leu211Gly Ala194Gln + Pro195Gly + Gly196Asn + Val197Cys + Asn198Gln 30 + Pro204Glu + Thr207Asp + Gly213Gln Pro195Glv + Asn198Asp + Gln200Glu + Tyr203Thr + Glv205Asn + Leu211Cvs + Asn212Ser + Gly213Gln Alai94Gly + Pro195Asn + Asn198Glu + Gln200Glu + Thr202Gln 35 + Gly205Ser + Thr207Pro + Gly213Gln Pro195Gly + Asn198Glu + Val199Gln + Gln200Asp + Thr202Gly + Pro204Gln + Thr207Pro + Leu211Cvs Pro195Asn + Gly196Gln + Asn198Glu + Gln200Asp + Thr202Gly + Tvr208Gln + Leu211Ser + Thr214Ser 40 Vall97Asn + Asn198Ser + Gln200Glu + Thr202Asn + Tyr203Cys + Pro204Ser + Gly205Pro + Tyr208Glu Ala194His + Val199His + Tyr203Asn + Tyr208His + Ala209Glu + Leu211Asp + Asn212Gln + Glv213Gln Gly196Gln + Val197Ser + Gln200Glu + Tyr203Val + Thr207Pro + Ala209Thr + Leu211Glu + Asn212Ser 45 Pro195Gln + Val199Gly + Gln200Asp + Pro204Asn + Gly205Asn + Tyr2081le + Ala209Pro + Leu211Glu Pro195Gln + Asn198Ser + Vall99Asn + Gln200Asp + Glv205Pro + Tyr208Ser + Leu211Glu + Thr214Asn Alal94His + Pro195Ser + Vall97Glu + Vall99Cys + Thr202Pro + Leu211Glu + Asn212Gln + Thr214Asn Ala194Ser + Pro195Gln + Asn198Ser + Gln200Asn + Gly205Gln + Leu211Asp + Asn212Gin + Gly213Glu Gly196Gln + Val199Gln + Tyr203Gly + Gly205Asn + Ala209His

	+ Leu211Asp + Asn212Gln + Gly213Asp		
	Asn198Gln + Gln200Ser + Tyr203Len + Gly205Asn	+	Thr207Glu
	+ Ala209Asp + Leu2llSer + Gly213Asp Ala194Ser + Pro195Ser + Val199Gln + Gln200Ser		esugares.
5	+ Ser210Asp + Asn212Glu + Thr214Gln	*	GIASOSCIU
3	Pro195Asn + Tyr203Cys + Pro204Gln + Tyr208Asn	4	Ala209His
	+ Ser210Asp + Asn212Asp + Thr214Gly		- X
	Gly196Asn + Vall99Ser + Thr202Gln + Pro204Ser	4	Thr207Gly
	+ Ser210Glu + Leu211Thr + Asn212Asp		_
10	Gly196Gln + Val197Cys + Asn198Ser + Pro204Gln	+	Thr207Asn
	+ Ala209Gln + Ser210Asp + Asn212Asp		
	Pro195Gly + Gly196Pro + Val197Cys + Asn198Ser	4	Gln200Asn
	+ Tyr208His + Ser210Asp + Asn212Glu		mb 0 0 7 0
15	Pro195Gln + Asn198Ser + Val199Gly + Thr202Pro + Tyr208Ile + Ser210Asp + Asn212Asp	.4-	rnrav/ber
13	Ala194Asn + Vall97Met + Vall99Thr + Ala209Asn		Caralaxan
	+ LeuZllVal + Asn2l2Glu + Gly2l3Gln	Ŧ	Servineb
	Ala194Gln + Pro195Asn + Val199Asn + Tyr203Ser		Thr207Asp
	+ Ser210Asp + Leu211Gly + Asn212Asp		
20	Vall99Cys + Gln200Ser + Thr202Asn + Gly205Asn	+	Thr207Gly
	+ Tyr208Asn + Ser210Glu + Asn212Asp		
	Ala194Thr + Val199Cys + Gln200Ser + Gly205Ser	4	Ser206Glu
	+ Tyr208Asp + Leu211Ala + Gly213Asn		w1 × 0 m n
~~	Ala194Pro + Val197Pro + Gln200Ser + Ser206Asp	Ť	ThrZ07Pro
25	+ Tyr208Asp + Ala209Pro + Thr214Gly Gly196Gln + Asn198Ser + Val199Met + Thr202Ser		Dre 2010 av
	+ Ser206Glu + Tyr208Glu + Asn212Gln	-	ELUKVAMON
	Pro195Asn + Gly196Asn + Val199Ala + Gln200Asn	+	Ser206Asp
	+ Thr207Asn + Tyr208Asp + Ala209Ser		
30	Gly196Asn + Tyr203Ala + Pro204Ser + Ser206Asp	+	Tyr208Asp
	+ Ala209Ser + Asn212Ser + Thr214Gln		
	Val197Gly + Asnl98Ser + Tyr203Asn + Pro204Gly	†	Gly205Ser
	+ Thr207Pro + Asn212Asp + Thr214Asp Ala194Gln + Val197Asp + Asn198Gln + Tyr203His		0++22.003.0
35	+ Leu211Ala + Gly213Ser + Thr214Asn	7	281510010
3.7	Ala194Pro + Val197Glu + Val199His + Gln200Ser	+	Tvr203His
	+ Pro204Asn + Tyr208Thr + Thr214Glu		
	Gly196Asn + Asn198Asp + Val199Gln + Gln200Ser	+	Thr202Ser
	+ Pro2045er + Leu211Cys + Gly213Glu		
40	Asn198Asp + Tyr203Met + Pro204Gly + Thr207Asn	÷	Tyr208Gln
	+ Ala209Glu + Asn212Ser + Thr214Ser		
	Asn198Glu + Val199Gly + Thr202Gly + Thr207Gln + Ala209Asp + Leu211Thr + Asn212Gln	4	Tyrzuecys
	Ala194His + Val197Asp + Asn198Gln + Gln200Glu	4	Thranakan
45	+ Tyr208Pro + Leu211Ser + Asn212Ser	•	111100011011
140	Pro195Gly + Gln200Asp + Tyr203Gly + Gly205Asn	4	Leu2llSer
	+ Asn212Glu + Gly213Gln + Thr214Gln		
	Ala194Asn + Gly196Ser + Val199Pro + Gln200Glu	+	Thr207Gly
	+ Tyr208Asn + Ala209Thr + Asn212Glu		
50	Ala194Thr + Val199Asn + Gln200Glu + Tyr203Gln	4	Pro204Gly
	+ Ala209His + Asn212Glu + Thr214Ser		Tu-2020
	Ala194Asn + Gly196Pro + Val197Ser + Asn198Gln + Pro204Asp + Tyr208Asn + Ala209Asp	.1.	igroupero
	Pro195Ser + Vall99Cys + Gln200Ser + Pro204Glu	+	Glv205Ser

	+ Tyr208Ala + Ala209Glu + Asn212Gln		
	Asnl98Gln + Vall99His + Thr202Gly + Pro204Glu	÷	Gly205Pro
	+ Tyr208Ala + Ala209Glu + Asn212Gln		01000
_	Gly196Ser + Asn198Ser + Val199Gly + Gln200Ser	+	Giyzubser
5	+ Tyr208Asp + Leu211Asp + Thr214Ser Pro195Gln + Gly196Asn + Val197Gly + Gln200Asn		W
	+ Thr207Gly + Ala209Asp + Asn212Glu	4	PLOZUMNII
	Ala194Ser + Gln200Ser + Gly205Ser + Ala209Asp	4	100211619
	+ Asn212Asp + Gly213Gln + Thr214Asn	•	neartrary
10	Ala194Gln + Pro195Gln + Gly196Pro + Tyr203Leu	ılı.	Drognaser
10	+ Ser206Asp + Ala209Glu + Leu211Pro	•	110503001
	Thr202Asn + Tyr203Ala + Pro204Ser + Ser206Asp	ą.	Tvr208Cvs
	+ Ala209Glu + Leu211Cys + Asn212Ser		.,
	Gly196Ser + Val199His + Gln200Asn + Gly205Asn	+	Ser206Glu
15	+ Ala209Asp + Leu211His + Asn212Ser		
	Ala194Asn + Val197Ala + Gln200Ser + Ser206Glu	+	Thr207Pro
	+ Ala209Glu + Asn212Gln + Gly213Asn		
	Pro195Gln + Val197Met + Val199Thr + Gln200Ser	+	Tyr203Ala
	+ Ala209Ser + Ser210Glu + Gly213Glu		*
20	Asn198Ser + Vall99Asn + Ala209Pro + Ser210Glu	+	Leu211Gly
	+ Asn212Ser + Gly213Asp + Thr214Gly		
	Ala194Gly + Asn198Gln + Tyr203Ala + Gly205Asp	+	Tyr208Gln
	+ Ala209Asp + Leu211Ala + Asn21ZGln		m) 0.000
	Alai94Gly + Gly196Gln + Thr202Gln + Tyr203Thr	+	ThrzU/Asp
25	+ Tyr208Thr + Ser210Glu + Asn212Ser		mt 2022
	Ala194Pro + Val197Thr + Tyr203Pro + Pro204Ser + Ser210Asp + Leu211Pro + Thr214Ser	÷	inizu/Asp
	Pro195Asn + Val199Ala + Thr202Ser + Gly205Gln	1	Thradan
	+ Ala209His + Ser210Glu + Gly213Asn	*	Mour or min
30	Pro195Gly + Glyl96Ser + Vall97Pro + Pro204Gly	+	Thr2076111
50	+ Tyr208Gln + Ala209His + Ser210Asp		
	Ala194Asn + Pro195Asn + Asn198Ser + Val199His	4	Thr207Asp
	+ Tyr208Val + Ala209Pro + Ser210Glu		
	Ala194Gly + Gly196Ser + Asn198Asp + Thr207Asn	÷	Ala209Gln
35	+ Leu211Pro + Gly213Gln + Thr214Asp		
	Ala194Gly + Pro195Ser + Vall97His + Asn198Asp	÷	Gln200Asn
	+ Pro204Ser + Asn212Ser + Thr214Asp		
	Vall99Asn + Gln200Glu + Pro204Gly + Gly205Asn	4-	Tyrzosser
	+ Leu211Ala + Asn212Ser + Gly213Glu Ala194Gln + Pro195Ser + Gly196Asn + Asn198Gln	4.	alwannal.
40	+ Tyr203Cys + Leu2llSer + Gly213Glu	,	GIHLOOGLU
	Ala194Ser + Gly196Asn + Vall97Thr + Asnl98Gln	+	Gln200Glu
	+ Thr207Asn + Tyr208His + Gly213Asp		
	Ala194Gln + Val197Gln + Asn198Asp + Gln200Asn	÷	Gly205Gln
45	+ Tvr208Asp + Leu211Gly + Thr214Ser		
	Ala194Ser + Asn198Ser + Thr202Pro + Pro204Asp	*	Gly205Gln
	+ Thr207Asn + Ser210Asp + Asn212Ser		
	Pro195Gln + Gly196Asn + Pro204Glu + Gly205Asn	+	Thr207Asn
	+ Tyr208Ser + Ala209Pro + Ser210Asp		
50	Ala194Thr + Gly196Pro + Val199Pro + Gln200Asn	÷	Pro204Glu
	+ Ala209Thr + Ser210Asp + Leu211Ala		m
	Alal94Ser + Gly196Gln + Val199Thr + Pro204Glu	*	TALTHOTTE
	+ Ala209Gln + Ser210Asp + Thr214Gly Ala194His + Val197Ser + Val199Ser + Gln200Ser	4	Pro2046311
	Wighadule + Agitaloet & Agitaboet & Grusaget	8	A A CARDAGA U

	+ Thr207Gly + Ala209Fro + Ser210Asp		
	Ala194Gin + Val197Ala + Asn198Ser + Pro204Asp	*	Tyrzuscys
	+ Ala209Gly + Ser210Asp + Asn212Ser		
	Gly196Ser + Vall97Thr + Asn198Ser + Gln200Glu	4-	Thr202Pro
5	+ Pro204Glu + Ala209Thr + Gly213Ser		
	Pro195Asn + Val197Pro + Val199Gly + Gln200Asp	+	ProZ04Glu
	+ Thr207Gly + Leu2llThr + Gly213Ser		
	Ala194Gln + Val197Asn + Gln200Ser + Thr202Gln	+	Thr207Glu
	+ Ala209Gly + Leu211Glu + Gly213Asn		
10	Ala194Ser + Gly196Ser + Val197Ser + Asn198Gln	4	G19205G1n
	+ Ser210Glu + Asn212Ser + Thr214Asp		
	Gly196Ser + Val199Cys + Gln200Ser + Thr207Pro	÷	Tyr208Pro
	+ Ala209Gly + Ser210Asp + Thr214Asp		
	Val197Cys + Val199Gly + Tyr203Gly + Tyr208Met	4	Ala209Ser
15	+ Ser210Glu + Leu211Ala + Thr214Glu		
	Ala194Pro + Pro195Ser + Gly196Ser + Val199Asn	÷	Thr202Gly
	+ Ser210Asp + Asn212Gln + Thr214Glu		
	Ala194Asn + Gly196Asn + Gln200Ser + Pro204Asn	*	Gly205Ser
	+ Ala209Ser + Ser210Asp + Thr214Asp		
20	Ala194His + Val197Cys + Tyr208Ile + Ser210Glu	÷	Leu211Gly
	+ Asn212Ser + Gly213Asn + Thr214Asp		
	Gly196Gln + Gln200Asn + Thr202Pro + Tyr203Cys	+	Gly205Gln
	+ Tyr208Ser + Ser210Glu + Thr214Asp		
	Asn198Gln + Val199Pro + Gln200Glu + Thr202Pro	ተ	Pro204Ser
25	+ Ser206Glu + Tyr208Gln + Thr214Asn		
	Pro195Gly + Gln200Asp + Tyr203Val + Ser206Asp	4	Tyr208Thr
	+ Leu211Gly + Asn212Gln + Gly213Asn		
	Gly196Gln + Gln200Glu + Thr202Gln + Tyr203Val	4	Ser206Glu
	+ Tyr208Val + Ala209Aan + Leu211Gly		
30	Pro195Gly + Gln200Glu + Thr202Pro + Gly205Ser	+	Ser206Glu
	+ Ala209Gln + Leu211His + Asn212Gln		
	Asn1986ln + Gln200Glu + Pro204Gly + Gly205Gln	4	Ser206Asp
	+ Tyr208Met + Asn212Ser + Thr214Asn		
	Ala194Pro + Pro195Gln + Gly195Ser + Val197His	4	GINZUUGIU
35	+ Gly205Ser + Ser206Glu + Leu211Ser		
	Ala194Gln + Gln200Asp + Tyr203Gln + Pro204Asn	4	Sersopein
	+ Tyr2081le + Ala209Gly + Gly213Asn		T- 004
	Ala194Gln + Pro195Gln + Val197His + Gln200Glu	4-	rrozu4ser
40	+ Ser206Asp + Tyr208Gln + Ala209Asn Pro195Gln + Val197His + Val199Asn + Gin200Asp		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
40	+ Ser206Glu + Leu211Thr + Thr214Pro	4	INIZUZPIO
	Pro195Gly + Asn198Gln + Val199Cys + Gln200Asp		**********
	+ Ser206Glu + Tyr208Cys + Gly213Ser	*	IIII AUAGI. Y
	Ala194Gly + Pro195Asn + Gly196Asn + Pro204Asp	_	Thr 2070
45	+ Leu211Glu + Asn212Gln + Thr214Asn	7,	1117 50 1981
4.2	T LEULIEUE T MONALAUEN T HIELIAMON		

TABLE 31

Loop 6 - Nonuple Mutation Variants

Ala194Gly + Pro195Ser + Val197Cys + Val199Asn + Gln200Asp + Tyr203Pro + Pro204Ser + Gly205Ser + Leu211Gln Alal94Pro + Gin200Asn + Thr202Asn + Tyr203Asn + Pro204Ser + Tyr208Asn + Ala209Asn + Ser210Asp + Thr214Gln

30

Pro195Gly + Vall99Ala + Gln200Ser + Thr202Gly + Gly205Pro + Ser206Glu + Ala209His + Leu211Ala + Gly213Asn

Prol95Gln + Gly196Gln + Val197Thr + Val199His + Thr202Gln + Tyr203Gly + Pro204Gly + Gly205Glu + Gly213Gln

5 Pro195Gly + Val197Gly + Val199Asn + Pro204Asn + Ser206Asp + Thr207Ser + Tyr208Gln * Ala209Gly + Thr214Asn

Ala194Thr + Val197Asn + Val199Pro + Gln200Asp + Thr202Ser + Tyr203Asn + Thr207Asn + Tyr208Leu + Ala209Gly

Pro195Asn + Gly196Asn + Asn198Gln + Tyr203Gln + Thr207Ser + Ala209Thr + Leu211Ala + Asn212Asp + Thr214Asn

Gly196Asn + Val199Gly + Tyr203Ser + Pro204Ser + Tyr208Gln + Ala209His + Asn212Ser + Gly213Asp + Thr214Gln

Pro195Ser + Val197His + Gln200Glu + Thr202Gln + Pro204Ser + Tyr208Val + Ala209His + Leu211Thr + Thr214Pro

Pro195Gly + Gly196Pro + Val199Thr + Thr202Pro + Tyr203Ile + Thr207Gly + Ala209Pro + Ser210Asp + Asn212Gln

Ala194Gly + Pro195Gln + Val197Asp + Tyr203Cys + Tyr208Val + Ala209Gln + Leu211Gly + Asn212Gln + Gly213Gln Gly196Asp + Asn198Gln + Thr202Gly + Thr207Asp + Tyr208Gly

+ Ala209Ser + Leu211Thr + Asn212Ser + Thr214Pro

25 Ala194Pro + Gly196Asn + Val197Met + Gln200Glu + Tyr203Gln + Gly205Asn + Tyr208Asn + Ala209Thr + Thr214Gln Ala194Pro + Gly196Gln + Val197Asn + Gly205Ser + Ser206Asp

Alaly4Fro + Gly19061f + Vall97Asf + Gly2055er + Ser20cAsp + Thr207Asf + Ala209Ser + Leu211Cys + Thr214Pro Gly196Gln + Vall97Thr + Gln200Ser + Tyr203Asf + Pro204Asf

+ Gly205Pro + Tyr208Ser + Ser210Glú + Asn212Ser Ala194Thr + Pro195Ser + Gly196Pro + Val197Cys + Gln200Glu + Pro204Ser + Gly205Asn + Ala209His + Leu211Pro

Pro195Gln + Gly196Asn + Asn198Gln + Val199Gln + Gln200Asp + Pro204Ser + Gly205Asn + Thr207Ser + Tyr208Ser

35 Alal94His + Val197Asn + Tyr203Gly + Pro204Gln + Thr207Gly + Ala209Gln + Leu211His + Asn212Gln + Gly213Gln

Ala194Ser + Pro195Gln + Val197Met + Val199His + Thr207Pro + Tyr208Ala + Asn212Gln + Gly213Glu + Thr214Asn Gly196Pro + Val197His + Asn198Gln + Gln200Glu + Tyr203Ser

Gly196Pro + Val197His + Ashi98Gin + Gin200Giu + Tyr203Set 40 + Gly205Pro + Thr207Ser + Leu211Thr + Gly213Ash

Gly196Ser + Val197Asn + Val199Thr + Thr202Gly + Tyr203Asn + Pro204Asn + Ala209Gln + Leu211Pro + Thr214Asp Ala194Thr + Pro195Ser + Val197Asn + Tyr203Met + Tyr205Ala

+ Ala209Ser + Asn212Gln + Gly213Asp + Thr214Asp

45 Ala194Asn + Gly196Gln + Val197Thr + Val199Ala + Gly205Asn + Ala209Pro + Leu211Asn + Gly213Glu + Thr214Asp Pro195Asn + Val199Met + Gln200Asn + Thr202Asn + Tyr203Cys

+ Ala209Ser + Leu211Gln + Gly213Asp + Thr214Glu Pro195Asn + Val197Met + Asn198Ser + Val199Asn + Gln200Asn

50 + Tyr208Gln + Leu211His + Giy213Glu + Thr214Asp Val197His + Val199Ala + Gln200Ser + Pro204Ser + Ala209Glu

+ Ser210Glu + Asn212Gln + Gly213Fro + Thr214Ser Gly19GGln + Val197Asn + Asn198Gln + Thr202Gly + Gly205Gln + Ala209Asp + Ser210Glu + beu211Net + Thr214Gly

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30

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Val197Cys + Asn198Ser + Val199Gln + Tyr203Gly + Pro204Gln + AlaZ09Glu + Ser210Glu + Gly213Pro + Thr214Gly

Pro195Asn + Val199His + Gln200Ser + Pro204Gin + Gly205Gln + Ala209Glu + Ser210Asp + Leu211Gln + Asn212Gln

5 Val197Asp + Asn198Glu + Val199Met + Thr202Gln + Pro204Ser + Gly205Gln + Thr207Gln + Tyr208His + Asn212Ser

Ala194Thr + Val197Glu + Asn198Asp + Val199His + Tyr203Asn + Tyr208His + Ala209Ser + Gly213Ser + Thr214Asn

Val197Cys + Asn198Ser + Val199Pro + Gln200Ser + Tyr203Ala + Tyr208Asn + Asn212Asp + Gly213Glu + Thr214Ser

Gly196Asn + Val197Met + Asn198Ser + Thr202Gly + Pro204Gln + Ala209Ser + Leu211His + Asn212Asp + Gly213Asp

Ala194Thr + Pro195Ser + Gln200Asn + Thr202Asn + Tyr203Gln + Tyr208Ser + Leu211Ala + Asn212Asp + Gly213Asp

Pro195Gln + Asn198Ser + Gln200Asn + Thr202Ser + Tyr203Met + Gly205Asp + Ser206Glu + Thr207Pro + Thr214Ser

Gly196Ser + Val199Thr + Gln20OAsn + Tyr203Ala + Gly205Asp + Ser206Asp + Tyr208Leu + Ala209Thr + Gly213Pro Ala194Pro + Gly196Ser + Val197Asn + Val199His + Gln20OAsn

+ Gly205Glu + Ser206Glu + Asn212Gln + Thr214Gln Ala194Thr + Val199Ser + Thr202Asn + Gly205Glu + Ser206Asp

+ Ala209Pro + Leu211Pro + Asn212Gln + Gly213Gln 25 Asn198Ser + Thr202Ser + Tyr203Ser + Pro204Gly + Gly205Asn

+ Ser206Asp + Thr207Glu + Ala209Pro + Thr214Ser Pro195Asn + Gly196Asn + Vai197Pro + Vai199Ser + Thr202Ser + Ser206Glu + Thr207Glu + Leu21IIIe + Gly213Ser

Thr202Ser + Tyr203Thr + Thr207Asp + Tyr208Glu + Ala209Pro + Leu211Val + Asn212Ser + Gly213Ser + Thr214Asn

Val199Pro + Gln200Ser + Thr202Ser + Thr207Asp + Tyr208Asp + Ala209Gly + Leu211Met + Asn212Ser + Thr214Pro Ala194Gln + Pro195Gly + Val197Ala + Gln200Glu + Tyr203Thr

+ Gly205Ser + Ala209Pro + Ser210Asp + Thr214Asn 35 Ala194Pro + Pro195Ser + Val199Met + Gln200Glu + Thr202Gly + Pro204Gln + Gly205Asn + Tyr208Gln + Ser210Asp

Ala194Gln + Val199Pro + Gln200Asp + Pro204Gly + Gly205Gln + Thr207Pro + Tyr208Asn + Ala209Gln + Ser210Asp

1820/F10 + 19/200889 # Ala200818 + Set210889 # Ala194Pro + Gly205487 + Asn198Gln + Gln200889 + Pro204Gly + Gly20588n + Tyr2081le + Set210889 + Asn212Set

Prol95Ser + Asn196Ser + Val199Ala + Gln200Glu + Tyr203Thr + Gly205Gln + Tyr208Met + Ser210Glu + Gly213Pro

Pro195Asn + Asn198Ser + Gln20GAsp + Thr202Gln + Tyr203Ala + Gly205Pro + Ser210Asp + Leu211Ser + Gly213Ser

5 Pro195Asn + Gly196Asn + Val197Ala + Asn198Ser + Gln200Asp + Tyr203Gln + Pro204Asn + Ala209Ser + Ser210Asp

Pro195Ser + Vall97Pro + Asn198Gln + Vall99Pro + Gln200Glu + Thr202Gln + Thr207Asn + Ala209Bls + Ser210Glu

Pro195Ser + Gly196Asn + Asn198Gln + Gln200Glu + Thr202Ser + Pro204Gly + Thr207Asn + Ser219Glu + Thr214Asn

Ala194Ser + Pro195Ser + Val197Mis + Val1997hr + Gln200Glu + Gly205Gln + Thr207Gly + Ser210Glu + Gly213Pro Pro195Msn + Val197Msp + Asn198Ser + Val199Msn + Thr207Pro

ro195Asn + Vall97Asp + Asn198Ser + Vall99Asn + Thr207Pro + Tyr208Ala + Leu211Val + Asn212Glu + Gly213Ser Pro195Asn + Gly196Asn + Val197Gin + Asn198Glu + Val199Thr + Tyr203Asn + Thr207Pro + Ser210Glu + Gly213Gln

Val197cys + Asn198Asp + Val199Ser + Tyr203Gln + Gly205Ser + Thr207Ser + Tyr208Leu + Ser210Asp + Leu211Gly

Ala194Pro + Gly196Gln + Val197Gly + Asn198Glu + Gln200Ser + Tyr203Thr + Pro204Ser + Ala209His + Ser210Glu

Gly196Ser + Val197His + Asn198Glu + Thr202Pro + Tyr203Ile + Thr207Asn + Tyr208Val + Ser210Glu + Thr214Ser

Gly196Asn + Val197Thr + Asn198Asp + Val199Ala + Pro204Asn + Ser210Asp + Leu211Val + Gly213Gln + Tbr214Pro

+ Ser210Asp + Leu211Vai + Gly213Gln + Thr214Pro
Gly196Ser + Asn196Glu + Thr202Asn + Gly205Ser + Thr207Gln

+ Tyr20811e + Ser210Glu + Leu211Ser + Asn212Ser Ala194Asn + Gly1967ro + Asn198Asp + Thr202Gly + Tyr208Ser + Ala209Pro + Ser210Glu + Leu211Ala + Thr214Asn

S Ala194His + Asn198Glu + Val199Gly + Gln200Asn + Gly205Asn + Ser210Glu + Leu211His + Asn212Gln + Thr214Ser

Ala194Gly + Asn198Glu + Gln200Asn + Thr202Pro + Tyr203Cys + Thr207Gln + Tyr208Met + Ser210Asp + Asn212Gln

Pro195Gly + Gly196Gln + Asn198Glo + Gln200Ser + Pro204Gln + Tyr208Leu + Ala209Thr + Ser210Glu + Leu211Tle

20 + Tyr208Leu + Ala209Thr + Ser210Glu + Leu211Tle Ala194Pro + Pro195Gln + Val197His + Asn198Glu + Thr202Gln + Gly205Pro + Thr207Asn + Tyr208Val + Leu211Asp

Pro195Gln + Asn198Glu + Thr202Ser + Tyr203Gly + Pro204Ser + Thr207Gln + Ala209Pro + Leu211Asp + Gly213Asn

5 Val199Asn + Gln200Asp + Thr202Gln + Tyr203Gly + Pro204Asn + Thr207Gln + Tyr208Ala + Ala209Glu + Asn212Ser

Gly196Pro + Val197Thr + Pro204Asp + Ser206Glu + Ala209Gln + Leu211Gln + Asn212Ser + Gly213Ser + Thr214Pro

Gly196Pro + Asn198Ser + Val199Thr + Pro204Glu + Ser206Asp + Thr207Gln + Ala209Glv + Asn212Ser + Thr214Glv

30 + Thr207Gln + Ala209Gly + Asn212Ser + Thr214Gly Ala194Asn + Vali197Gly + Gln200Ser + Thr202Ser + Pro204Asp + Ser206Asp + Tyr208Gln + Ala209Gln + Leu211Gly Ala194Pro + Thr202Gln + Tyr203Asn + Pro204Asp + Ser206Glu

+ Tyr208Gly + Ala209Ser + Gly213Pro + Thr214Pro Ala194Asn + Pro195Gln + Val197Thr + Asn198Ser + Pro204Asp

+ Gly205Ser + Ser206Asp + Asn212Ser + Thr214Asn Pro195Gly + Gln200Ser + Thr202Gln + Tyr203Pro + Pro204Asp

+ Gly205Asn + Ser206Glu + Thr207Asn + Leu211His

Ala194His + Gly196Asn + Val197Met + Asn198Ser + Pro204Asp 40 + Ser206Asp + Leu211Asn + Asn212Ser + Thr214Gln Asn198Gln + Val199Cvs + Gln2008er + Thr202Gln + Fro204Asp

+ Gly205Gln + Ser206Asp + Tyr208Leu + Thr214Pro

Ala194His + Pro195Ser + Gly196Pro + Asn198Gln + Pro204Glu + Ser206Asp + Thr207Pro + Tyr208His + Ala209Asn

45 Ala194Ser + Asn198Asp + Gln200Ser + Thr202Gly + Thr207Pro + Tyr208Asn + Ala209Gln + Leu211Ser + Asn212Glu

Gly196Asn + Asn198Gln + Gln200Asn + Tyr203Thr + Pro204Ser + Gly205Asp + Thr207Glu + Ala209Ser + Thr214Asn

Vall97His + Asn198Gln + Vall99Met + Gln200Ser + Pro204Glu 50 + Glv205Ser + Thr207Glu + Tyr208Val + Thr214Gly

Vall97Asn + Asn198Asp + Vall99Ala + Gln200Glu + Tyr203Cys + Pro204Gly + Gly205Asn + Thr207Gln + Gly213Asn

Pro195Asn + Gly196Gin + Asn196Asp + Val199Pro + Gln200Glu + Tvr203Vai + Gly205Asn + Tvr200Cys + Ala209Pro WO 95/39011 PCT/US95/04760

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Pro195Gly + Gly196Pro + Val197Asp + Thr202Ser + Pro204Gln + Thr207Gly + Tyr2081le + Asn212Gln + Gly213Glu

Ala194Pro + Val197Glu + Tyr203His + Gly205Pro + Thr207Gly + Ala209Asn + Leu211His + Gly213Asp + Thr214Gly

Pro195Gln + Val197Glu + Asn198Gln + Val199Ala + Pro204Ser + Gly205Gln + Ala209Ser + Gly213Glu + Thr214Ser

Pro195Asn + Val197Asp + Asn198Gln + Val199Ser + Gln200Ser + Thr207Ser + Tyr208Ile + Asn212Ser + Glv213Asp

Gly196Pro + Val197Glu + Asn198Gln + Val199Asn + Pro204Gly

+ Thr207Pro + Leu211His + Gly213Asp + Thr214Asn Ala194Ser + Asn198Gln + Thr202Pro + Tyr203Met + Pro204Ser

+ Thr207Gln + Ala209Asp + Leu211Glu + Thr214Gln

Gly196Pro + Val197Pro + Thr202Asn + Tyr203Cys + Tyr208Gln + Ser210Asp + Asn212Asp + Gly213Pro + Thr214Ser

5 Pro195Gln + Tyr203Thr + Gly205Gln + Ala209Gln + Ser210Asp + Leu21lAsn + Asn212Glu + Gly213Asn + Thr214Gln Ala194Gly + Pro195Gur + Vall278 + Thr202Gly + Dra204Gly

Ala194Gly + Pro195Ser + Vall97His + Thr202Gln + Pro204Gly + Ser210Asp + Leu211His + Asn212Glu + Thr214Gly

Pro195Asn + Gly196Asn + Val197Asn + Thr202Ser + Tyr203Val + Gly205Ser + Ser210Asp + Asn212Glu + Gly213Pro

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Gln200Ser + Thr202Gly + Tyr203Leu + Thr207Pro + Tyr208Pro + Ser210Asp + Leu211Pro + Asn212Glu + Thr214Gly

Ala194Gln + Gly196Ser + Val197Cys + Val199Met + Tyr203Leu

+ Ala209Thr + Ser210Asp + Asn212Glu + Thr214Ser 5 Val197Met + Val199Ala + Gln200Asn + Tyr203Thr + Thr207Gln

+ Tyr208Glu + Ser210Glu + Asn212Ser + Thr214Gly Gly196Ser + Val197Ala + Val199Ser + Thr202Gly + Tyr203Cys

+ Gly205Asn + Ser206Glu + Tyr208Asp + Leu211Ile Ala194Gly + Pro195Ser + Val199His + Thr202Asn + Gly205Gln

+ Sex206Asp + Tyx208Glu + Asn212Ser + Thr214Pro Gly196Pro + Val199Gln + Thr202Ser + Gly205Pro + Ser206Asp + Thr207Gln + Tyr208Glu + Leu211His + Asn212Ser

Val197His + Asn198Ser + Gly205Ser + Thr207Pro + Tyr208Val + Leu211Val + Asn212Glu + Gly213Ser + Thr214Glu

35 Pro1955er + Gly196Pro + Val199Thr + Tyr203Gr + Tyr208Gly + Ala209Ash + Ash212Glu + Gly213Ser + Thr214Glu

Pro195Asn + Asn198Gln + Gln200Asn + Thr202Asn + Thr207Asn + Tyr208Gln + Asn212Glu + Gly213Ser + Thr214Glu

Alal94Asn + Vall99Ser + Thr202Gly + Pro204Asn + Gly205Ser

+ Ala209Asn + Leu2llAsn + Asn212Asp + Thr214Glu

Ala1945er + Gly196Gln + Pro204Asp + Gly205Pro + Thr207Pro + Tyr208Glu + Leu211Ile + Gly213Asn + Thr214Ser

Pro195Ser + Val197Asp + Asn198Gln + Gln200Asn + Tyr203Pro + Gly205Asn + Ser210Asp + Asn212Ser + Thr214Asn

5 Ala194His + Gly196Ser + Val197Asp + Asn198Ser + Gln200Asn + Thr202Ser + Gly205Gln + Ser210Glu + Asn212Ser

Ala194Thr + Val197Glu + Thr202Gln + Pro204Gln + Tyr208Gly + Ala209Thr + Ser210Glu + Asn212Ser + Thr214Gln

Gly1965er + Val197Asp + Val199Pro + Tyr203Cys + Pro204Ser 50 + Thr207Asn + Tyr208Asn + Ser210Asp + Asn212Ser

Ala194Pro + Pro195Ser + Gly196Gln + Val197Asp + Val199Met + Gln200Asn + Leu211Met + Gly213Pro + Thr214Asp

Pro195Asn + Gly196Gln + Asn198Gln + Val199Ala + Gln200Ser + Tyr203Pro + Gly205Glu + Thr207Asn + Tyr208Asp

Gly196Pro + Asn198Ser + Val199Asn + Thr202Gly + Pro204Gln + Gly205Asp + Thr207Gln + Tyr208Asp + Thr214Asn

Val197Ser + Asn198Glu + Gln200Asn + Tyr203Gln + Pro204Asn + Glv205Pro + Thr207Glv + Ala209Thr + Glv213Glu

5 Alal94Thr + Gly196Gin + Val197His + Asn198Asp + Val199Ser + Tyr203Pro + Tyr208Cys + Gly213Asp + Thr214Pro

Asn196Asp + Gln200Ser + Tyr203Gln + Pro204Ser + Gly205Asn + Thr207Asn + Ala209Glu + Leu211Gln + Asn212Ser

Pro195Gly + Gly196Asn + Asn198Glu + Thr202Gln + Tyr203Ala

+ Pro204Ser + Thr207Pro + Ala209Glu + Gly213Gln Ala194Pro + Asn198Glu + Val199Thr + Pro204Gly + Thr207Gly

+ Tyr2081le + Ala209Asp + Leu211Met + Asn212Ser Ala194Ser + Val197Glu + Val199Thr + Gln200Asp + Tyr203Gly + Gly205Ser + Tyr208His + Ala209Thr + Asn212Ser

15 Glyl96Gln + Val197Glu + Val199Pro + Gln200Asp + Gly205Gln + Thr207Ser + Ala209Thr + Leu211Pro + Thr214Gly

+ INTACASET + ANAZOSTAT + LEUZITFTO + INTZIGGTY
Vall97Gly + Gln200Glu + Thr20ZGly + Tyr203Leu + Gly205Gln
+ Thr207Glv + Tyr208Leu + Ala209Asn + Asn21ZAsp

Pro1955er + Gly196Asn + Asn198Ser + Val199His + Gln200Glu + Tyr203Pro + Ala209Ser + Asn212Asp + Thr214Asn

20 + Tyr203Fro + Aia209Ser + Asn212Asp + Thr21dAsn Asn198Ser + Val199Met + Gln200Glu + Thr202Ser + Tyr2031le + Glv205Fro + Ala209Fro + Asn212Glu + Glv213Gln

Gly196Pro + Vall97Ser + Vall99Pro + Gln200Glu + Ala209Gly

+ Leu211Gln + Asn212Asp + Gly213Pro + Thr214Asn 25 Ala194Gln + Gly196Ser + Val197Pro + Thr202Pro + Pro204Asp

+ Tyr208Gly + Ala209Glu + Gly213Asn + Thr214Pro
Ala194Pro + Val197Ser + Val199His + Gln200Asn + Pro204Gly
+ Ser206Glu + Thr207Asn + Tvr208Leu + Ala209Glu

Gly196Asn + Thr202Asn + Pro204Asn + Gly205Pro + Ser206Glu + Tyr208Asn + Ala209Asp + Leu211Met + Thr214Gln

Pro195Gly + Asn198Gln + Val199Ser + Gln200Ser + Tyr203Thr + Gly205Pro + Ser206Glu + Ala209Glu + Thr214Asn

Ala194Thr + Val197Ala + Thr202Ser + Tyr203Fro + Gly205Asn + Ser206Glu + Ala209Glu + Leu211Gln + Thr214Asn

Ala194Thr + Val199Asn + Thr202Pro + Tyr203Tle + Pro204Asn + Ser206Asp + Thr207Asn + Ala209Glu + Thr214Asn

Ala194Ser + Pro195Asn + Val197Gly + Val199Gly + Gln200Glu 40 + Thr202Gln + Pro204Asn + Thr207Asp + Leu211Gln

Ala194Gly + Val197His + Gln200Ser + Pro204Asn + Thr207Ser + Ser210Glu + Leu211Gly + Glv213Glu + Thr214Asn

Ala194Gln + Gly196Gln + Val197Met + Val199His + Thr202Pro + Gly205Asn + Ala209Ser + Ser210Glu + Gly213Glu

+ Giy205Asn + Ala2095er + Ser210Gin + Giy213Gin 45 Pro195Asn + Val197Thr + Val199Ala + Gln200Asn + Tyr203Asn + Thr207Gly + Ser210Asp + Asn212Gin + Gly213Glu

Ala194His + Val199Pro + Gln200Asn + Thr202Pro + Tyr203Asn + Gly205Glu + Ala209Glu + Asn212Gln + Thr214Asn

Gly196Pro + Asnl98Gln + Gln200Asn + Tyr203Gln + Pro204Gln 0 + Gly205Asp + Ala209Glu + Asn212Gln + Thr214Gln

Pro195Gln + Asn198Gln + Val199Ala + Gln200Asn + Thr207Glu + Tyr208Leu + Ala209Ser + Ser210Asp + Gly213Pro

Pro195Gly + Gly196Gln + Val199Ser + Gln200Asn + Pro204Ser + Gly205Ser + Thr207Glu + Ser210Glu + Thr214Pro

Gly196Gln + Gln2005er + Thr202Gly + Tyr203lle + Thr207Rsp + Tyr208lle + Ser210Asp + Leu211Ran + Asn212Ser Ala194His + Gly196Gln + Val197Gly + Thr2707Glu + Tyr208Va1

+ Ala209Gln + Ser210Asp + Leu211His + Gly213Ser

Ala194Gln + Asn198Asp + Val199Ser + Gln200Ser + Tyr2031le + Gly205Asn + Thr207Asn + Asn212Gln + Thr214Asp

Val197Pro + Asn198Glu + Val199Thr + Gln200Ser + Pro204Asn + Gly205Pro + Leu211Cys + Asn212Ser + Thr214Asp

Ala194Ser + Val199Thr + Gln200Glu + Tyr203Cys + Tyr208Gly

+ Ala209His + Leu2l1Gly + Asn212Ser + Gly213Glu

Gly196Gln + Asn198Gln + Val199Met + Gln200Asp + Pro204Gln + Tyr208Pro + Asn212Gln + Gly213Asp + Thr214Gln

Vall97Asp + Vall99Gin + Gh200Ser + Thr204Fr + Ala209Glu + Leu211Gly + Asn212Ser + Gly213Gln

5 Ala194Ser + Gly196Pro + Val197Glu + Asn198Ser + Val199Met + Pro204Gly + Thr207Gln + Ala209Glu + Gly213Gln

Val197Asp + Asn198Ser + Pro204Gln + Gly205Gln + Thr207Gly + Tyr208Met + Ala209Glu + Asn212Gln + Thr214Gln

Ala194Ser + Val197Glu + Asn198Gln + Tyr203Asn + Gly205Asn + Ala209Glu + Asn212Gln + Gly213Ser + Thr214Pro

20 + Ala209Glu + Asn212Gln + Gly213Ser + Thr214Pro Pro195Gly + Val197Ser + Asn198Ser + Tyr203Leu + Pro204Glu

+ Ser210Asp + Leu211Ser + Asn212Ser + Thr214Gln Ala194Asn + Pro195Gln + Asn198Gln + Val199Asn + Gln200Asn

+ Pro204Asp + Thr207Pro + Ser210Glu + Gly213Gln

is Ala194Pro + Val197Ser + Asn198Ser + Thr202Pro + Tyr203Val + Pro204Glu + Ser210Asp + Asn212Ser + Thr214Asn

Ala194Gln + Pro195Ser + Gly196Pro + Val199Ser + Pro204Asp + Tyr208Cys + Ala209Thr + Ser210Glu + Gly213Asn

Pro195Ser + Tyr203Pro + Pro204Asp + Gly205Pro + Thr207Gln + Ala209Gly + Ser210Asp + Leu211Asn + Thr214Asn

Gly196Ser + Asn198Ser + Thr202Pro + Pro204Asp + Tyr208Val + Ala209Gln + Ser210Asp + Leu211Asn + Asn212Gln Gly196Ser + Val199Met + Tyr203Ala + Pro204Glu + Gly205Ser

+ Thr207Ser + Tyr208Leu + Ala209Gln + Ser210Asp

Ala194Asn + Gly196Ser + Asn198Ser + Val199Met + Gln200Asn + Thr202Gly + Thr207Gln + Ala209Asp + Gly213Asp

Ala194Gln + Pro195Gln + Thr202Ser + Pro204Asn + Ala209Thr

+ Ser210Glu + Leu211Asn + Gly213Gln + Thr214Glu Gly196Gln + Val197Pro + Asn198Gln + Val199Gly + Ala209Pro

+ Ser210Asp + Leu211Cys + Asn198G1R + Val198G1y + Ata208FRC

Ala194Asn + Pro195Gly + Asn198Gln + Val199His + Tyr203Pro + Thr207Gly + Tyr208Met + Ser210Asp + Thr214Asp

+ Thrzo/Gly + Tylzomet + Setzlomsp + Intzlamsp 45 AlaigaPro + ProigsSer + Glylg6Asn + Thrzo2Gly + Pro204Ser

+ Ala209His + Ser210Glu + Leu211Ser + Thr214Asp Ala194Thr + Gly196Pro + Asn198Ser + Thr207Asn + Tyr208Ile

+ Ser210Asp + Leu211Val + Gly213Gln + Thr214Glu Ala194Gly + Pro195Ser + Asn198Ser + Thr202Ser + Gly205Ser

50 + Ala209Gln + Ser210Asp + Asn212Ser + Thr214Asp Ala194Ser + Pro195Gly + Gly196Ser + Val199Ala + Tyr203Gln

+ Pro204Gln + Thr207Ser + Ser210Glu + Thr214Glu Gly196Ser + Gln200Asn + Thr202Pro + Tyr203Leu + Thr207Gln

+ Ser210Asp + Leu211Ala + Gly213Pro + Thr214Asp

- Ala194Gln + Asn198Ser + Val199Thr + Gln200Ser + Tyr203Thr + Ala209Pro + Ser210Asp + Leu211Ash + Thr214Glu
- Pro195Gln + Gly196Gln + Tyr203Cys + Pro204Ser + Gly205Pro + Tyr208His + Ala209Thr + Ser210Asp + Thr214Glu
- Glyl96Gln + Asni985er + Vali99Thr + Gln2005er + Thr202Ser + Thr207Ser + Ala209His + Ser210Glu + Thr214Glu
 - Pro195Asn + Gly196Pro + Asn198Gln + Tyr203Ala + Thr207Ser + Ala209Pro + Ser210Asp + Leu211Thr + Thr214Asp
- Ala194Ser + Pro195Asn + Val199Pro + Pro204Asn + Gly205Gln + Thr207Gln + Ser210Glu + Gly213Ser + Thr214Asp
 - Gly196Ser + Val197Asn + Thr202Gln + Tyr203Ser + Pro204Ser + Gly205Ser + Ser210Glu + Leu211Cys + Thr214Asp
 - Val197Asn + Gln200Asp + Tyr203Cys + Pro204Asn + Gly205Asn + Ser206Asp + Thr207Ser + Tyr208Leu + Asn212Gln
- - Ala194Gln + Pro195Gln + Gly196Asn + Val199Ser + Gln200Asp + Thr202Ser + Glv205Ser + Ser206Glu + Ala209Ser
 - Pro195Asn + Gly196Fro + Val197Cys + Val199Met + Gln200Asp + Ser206Glu + Thr207Ser + Ala209Gln + Leu211Val
 - Pro195Gly + Val199Pro + Gln200Asp + Thr202Ser + Tyr203Gly + Pro204Gln + Ser206Asp + Leu211Met + Asn212Ser Glv196Pro + Val197Cvs + Asn198Gln + Gln200Glu + Thr202Asn
- + Ser206Asp + Ala209Ash + Leu21lCys + Gly213Ser - Pro195Gin + Asn198Ser + Gln200Glu + Thr202Ash + Pro204Gly
- + Ser206Asp + Thr207Ser + Tyr208Ser + Ash212Gln
 Gly196Asn + Ash198Ser + Vai199Met + Gln200Asp + Thr202Ser
 + Tyr203His + Pro204Bsh + Gly205Gln + Ser206Glu
- # 197203813 * F1020485H * G192038H * Se120881H * Ala194Thr + Asn198Gln + Val199Ala + G1n200Asp + Thr202Asn + Ser206Glu + Thr207Ser + Tvr208His * G19213Gln
- Ala194Gln + Gly196Gln + Asn198Gln + Gln200Asp + Thr202Asn + Ser206Glu + Thr207Ser + Tyr208Thr + Gly213Gln

TABLE 32

Loop 6 - Decuple Mutation Variants

- Ala194Ser + Gly196Gln + Val197Ala + Asn198Gln + Thr202Pro + Pro204Ser + Gly205Ser + Thr207Pro + Leu211Val + Asn21Z8sp
- Pro195Ser / Val197Gln + Val199His + Thr202Asn + Tyr203Pro 40 + Gly205Gln + Ala209Thr + Ser210Glu + Asn212Ser + Thr214Gln
 - Ala194Gly + Asn196Ser + Val199Ala + Thr202Gln + Tyr203Leu + Pro204Gly + Gly205Pro + Ala209His + Gly213Ser + Thr214Asp
- 45 Ala194His + Gly196Gln + Thr202Gly + Tyr203Val + Gly205Asn + Thr207Gln + Tyr208Cys + Ala209Sez + Gly213Gln + Thr214Asn
 - Alai94Thr + Prol95Ser + Gly196Asn + Asn198Glu + Gln200Asn + Thr202Gly + Pro204Ser + Asn212Gln + Gly213Pro + Thr214Gly
- 50 Thr214Gly Ala194Ser + Pro195Asn + Glyl96Asn + Vall99Thr + Thr202Gln + Pro204Asp + Thr207Asn + Tyr206Ser + Leu211Asn +

PCT/US95/04768 WO 95/38011

Asn212Gln

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Pro195Asn + Glv196Ser + Val197Glv + Asn198Ser + Thr202Glv + Gly205Pro + Thr207Pro + Tyr208Asp + Ala209Ser + Thr214Agn

- Ala194His + Pro195Gln + Gly196Asn + Asn198Gln + Val199His + Pro204Ser + Glv205Asn + Thr207Ser + Tvr208Ser +
 - Ala194Pro + Pro195Asn + Val197Asn + Val199Cvs + Gln200Ser + Thr202Pro + Pro204Ser + Ser206Glu + Tyr208His + Leu211Ile
- 10 Alal94Thr + Val197Met + Asn198Asp + Val199Gly + Gln200Ser + Tvr203Gln + Pro204Asn + Thr207Gln + Ala209Pro + Leu211Ala
- Ala194Pro + Pro195Gly + Vall97Asn + Asn198Ser + Vall99His 15 + Tyr208His + Ala209Asp + Leu211Thr + Asn212Gln +
 - Pro195Ser + Val199Met + Thr202Ser + Tyr203Ile + Gly205Gln + Ser206Asp + Tyr208His + Leu211Pro + Asn212Gln +
- Glv213Pro Ala194Thr + Val197Ser + Val199Asn + Thr202Gln + Tvr203Met + Glv205Pro + Ser206Glu + Tvr208Ile + Ala209Asn +
- G1v213Ser Alai94Thr + Val197Gln + Asn198Gln + Val199Gly + Thr202Ser + Pro204Ser + Gly205Pro + Thr207Asn + Ala209Pro +
 - Ala194His + Pro195Asn + Glv196Asn + Val199Thr + Gln200Asn + Thr202Asn + Tyr203Ala + Gly205Asp + Thr207Gly +
 - Thr214Pro Ala194Ser + Pro195Gly + Gly196Ser + Val197Pro + Asn198Gln + Val199Thr + Thr202Pro + Tvr203Met + Pro204Gln +
 - G1v205G1n Alal94Thr + Pro195Gln + Vall97Asp + Gln200Ser + Thr202Pro + Pro204Ser + Gly205Gln + Thr207Glv + Tyr208His + Ala209G1v
- Ala194Pro + Pro195Ser + Asn198Ser + Val199Gln + Gln200Asp 35 + Thr202Gln + Tyr203Asn + Pro204Gly + Leu211Val + Thr214Pro
 - Pro195Ser + Glv196Gln + Val199Pro + Gln200Asn + Tyr203Gln + Thr207Asp + Ala209His + Leu211His + Asn212Gln +
- 40 Thr214Gly Gly196Pro + Asn198Ser + Val199Gly + Gln200Ser + Thr202Asn + Tyr203Ser + Tyr208Leu + Ala209His + Leu211Asp + Asn212Asp
- Glv196Asn + Val199Ala + Gln200Ser + Thr202Gln + Tvr203His + Pro204Asn + Glv205Pro + Asn212Gln + Glv213Glu + 45 Thr214Glu
 - Gly196Pro + Val199Ser + Gln200Ser + Thr202Pro + Pro204Gln + Ala209Glu + Ser210Glu + Asn212Ser + Sly213Ser + Thr214Ser
- Val197Thr + Asn198Gln + Val199Gln + Pro204Gly + Thr207Pro + Ala209Asp + Ser210Glu + Asn212Ser + Glv213Ser + Thr214Ser
 - Ala194Pro + Pro195Gln + Val197Ala + Val199Gln + Gln200Ser + Pro204Gln + Gly205Pro + Tyr208Met + Ala209Asp +

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Ser210Glu

- Pro195Gly + Val197Gly + Asn198Gln + Thr202Gly + Tyr203Ala + Gly205Pro + Ala209Glu + Ser210Glu + Leu211Ser + Gly213Gln
- 5 Pro195Ser + Gly196Asn + Asn198Gln + Gin200Ser + Thr202Gly + Pro204Gln + Tyr208Thr + Leu211Cys + Asn212Glu + Gly213Glu
 - Gly196Gin + Val197Ser + Gln200Ser + Thr202Pro + Pro204Asp + Gly205Asp + Tyr208Gin + Ala209Pro + Asn212Ser + Thr214Gin
- 10 Thr214Gln Ala194Fro + Pro195Gln + Gly196Gln + Pro204Asp + Gly205Glu + Tyr208Ala + Ala209Ser + Leu211Asn + Gly213Asn + Thr214Ser
- Ala194Thr + Val197Cys + Val199Met + Gln200Ser + Gly205Pro + Tyr208Thr + Ser210Glu + Leu211Asp + Asn212Ser + Gly213Pro
 - Alal94Gly + Val197His + Thr202Ser + Tyr203Asn + Thr207Pro + Tyr208Cys + Ser210Glu + Leu211Glu + Asn212Gln + Gly213Pro
- 20 Val197His + Asn198Ser + Gln200Ser + Thr202Asn + Gly205Ser + Tyr208Gln + Ser210Glu + Leu211Glu + Asn212Ser + Thr214Pro
 - Ala194Thr + Gly196Asn + Asn198Gln + Gln200Asn + Thr202Pro + Tyr203Thr + Gly205Asn + Ser210Glu + Leu211Glu + Asn212Ser
 - Ala194Gly + Gly196Gln + Asn198Ser + Val199Cys + Pro204Asn + Gly205Asp + Ser206Asp + Thr207Gln + Ala209Gly + Gly213Asn
 - Pro195Gln + Val197Met + Val199Ala + Gln200Ser + Gly205Asp + Ser206Asp + Thr207Asn + Tyr208Gln + Leu211Pro + Asn212Ser
 - Ala194His + Pro195Gln + Asn198Gln + Thr202Pro + Gly205Glu + Ser206Asp + Thr207Pro + Leu211Thr + Gly213Ser + Thr214Gln
- 35 Gly196Pro + Asn198Gln + Val199Gly + Gln200Ser + Thr202Asn + Pro204Asn + Gly205Glu + Ser206Asp + Thr207Gly + Thr214Gln
- Pro195Gln + Val197His + Asn198Gln + Thr202Gly + Gly205Asp + Ser206Glu + Thr207Ser + Tyr208Ala + Asn212Gln + 40 Gly213Asn
 - Ala194Asn + Gly196Asn + Val197Ser + Asn198Ser + Val199Met + Thr202Asn + Tyr203Ala + Gly205Asp + Ser205Asp + Thr214Asn
- Alai94Thr + Pro195Asn + Gly196Gln + Val199Thr + Gln200Asn 45 + Thr202Ser + Pro204Asn + Gly205Asp + Ser206Glu + Thr207Asn
 - Pro195Ser + Gly196Ser + Val197Pro + Asn198Gin + Gln200Asn + Tyr203Leu + Gly205Asp + Ser206Glu + Asn212Ser + Thr214Pro
- - Alai94Gly + Gly196Gln + Gin200Ser + Thr202Ser + Pro204Asn + Ser206Asp + Thr207Asp + Ala209Gln + Leu211Met +

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Thr214Pro Gly196Asn + Val197Ser + Val199Ala + Tyr203Ile + Ser206Asp + Thr207Glu + Ala209Ser + Leu21lAla + Asn212Ser + Thr214Asn

- Ala194Ser + Pro204Asn + Gly205Ser + Ser206Asp + Thr207Glu + Tyr208Met + Ala209Asn + Leu211Ile + Asn212Gln +
 - Alal94Gln + Asn198Gln + Val199Asn + Thr202Gln + Tvr203Ile + Gly205Gln + Ser206Asp + Thr207Glu + Tvr208Ser + G1v2135er
 - Gly196Gln + Asn196Gln + Thr202Gln + Pro204Ser + Gly205Ser + Ser206Glu + Thr207Asp + Leu211Ile + Gly213Pro + Thr214Pro
- Pro195Asn + Glv196Gln + Vall97Gln + Thr202Asn + Glv205Ser 15 + Ser206Glu + Thr207Glu + Tvr208Ile + Glv213Gln +
 - Asn198Ser + Thr202Ser + Tvr203Ile + Gly205Asn + Thr207Asn + Tyr208Asp + Ala209Glu + Leu211Ile + Gly213Ser + Thr214Ser
- Val199His + Gln200Glu + Tvr203Met + Pro204Glv + Thr207Pro + Ala209Thr + Ser210Glu + Leu211Asn + Asn212Ser + Gly213Pro
 - Alal94His + Glv196Ser + Asn198Ser + Gln200Glu + Thr202Gln + Tyr203Gln + Gly205Pro + Thr207Glv + Ser210Glu + Gly213Asn
- Gly196Pro + Val199Asn + Gln200Glu + Pro204Gly + Tyr208His + Ser210Asp + Leu211Gln + Asn212Ser + Gly213Gln + Thr214Asn
 - Pro195Glv + Glv196Pro + Gln200Aso + Tvr203Aso + Pro204Aso + Gly205Asn + Thr207Asn + Tyr208Ile + Ser210Asp + Glv213Gln
 - Alal94Gln + Pro195Gln + Gly196Gln + Val197Gln + Gln200Asp + Thr207Glv + Ala209Asn + Ser210Asp + Leu211Glv + Gly213Asn
- Vall97Thr + Vall99Ser + Gln200Glu + Tyr203Asn + Pro204Gly + Thr207Asn + Tyr208Gly + Ser210Glu + Asn212Ser + Thr214Asn
 - Glv196Gln + Val197Gln + Val199Asn + Gln200Glu + Tvr203Asn + Thr207Gln + Ala209Glv + Ser210Glu + Asn212Gln +
 - Gly213Gln Pro195Asn + Val197Met + Val199Cys + Gln200Asp + Thr202Asn + Thr2075er + Tyr208Gly + Ala209Gln + Ser210Glu + Leu211Asn
 - Alai94Asn + Vali99Gln + Gln200Asp + Tvr203Glv + Pro204Ser + Glv205Pro + Tvr208Ile + Ser210Glu + Leu211Asn + Glv213Ser
 - Alal94His + Pro195Gln + Val197Glu + Asn198Ser + Val199Ser + Tyr203His + Thr207Pro + Leu211Gln + Asn212Glu + Gly213Ser
- Gly196Ser + Val197Glu + Asn198Gln + Val199Cys + Tyr203Pro + Pro204Gly + Ala209Gln + Asn212Glu + Gly213Gln + Thr214Asn
 - Gly196Ser + Vall97Gly + Asn198Asp + Gln200Ser + Tyr203Pro + Tvr208Ala + Ala209Glv + Ser210Glu + Leu21111e +

Thr214Asn Glv196Pro + Asn198Asp + Val199Gln + Gln200Asn + Pro204Gln + Glv205Pro + Thr207Gly + Ser210Asp + Asn212Gln +

03

Gly213Ser Pro195Asn + Gly196Ser + Val197Gln + Asn198Glu + Gln200Ser + Pro204Gly + Tyr208Gln + Ala209Asn + Ser210Glu +

Asn198Asp + Val199Met + Gln200Asn + Thr202Gln + Pro204Asn + Gly205Gln + Tyr208Ala + Ala209His + Ser210Glu +

Thr214Pro \$63 Ala194Gln + Val197Ala + Asni98Glu + Gln200Asn + Thr202Gly + Pro204Gln + Gly205Gln + Tyr208Thr + Ser210Asp +

Leu211Val

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Val197Ser + Asn198Asp + Val199Asp + Gln200Ser + Pro204Ser + Thr207Pro + Tvr208Leu + Ser210Glu + Asn212Gln + 15 Thr214Ser

Ala194Thr + Glyl96Asn + Vall97Ser + Asn198Glu + Vall99Asn + Gln200Ser + Thr202Ser + Thr207Ser + Ser210Glu + Glv2135er

Gly196Pro + Vall97Met + Asnl98Asp + Vall99Gly + Gln200Asn 20 + Tyr203Pro + Gly205Asn + Tyr208Val + Ser210Asp + Len211His

Gly196Gln + Asn198Asp + Gln200Asn + Tyr203Asn + Gly205Pro + Thr207Ser + Tyr208Gln + Ala209Pro + Leu211Glu + Asn212Gln

Pro195Asn + Val197Pro + Asn198Glu + Val199Cys + Tyr203Asn + Thr207Glv + Tvr208Gln + Ala2095er + Leu211Glu + Glv213Asn

Ala194Gin + Gly196Gin + Val199Met + Gln200Asp + Tyr203Cys + Thr207Ser + Ala209Asp + Asn212Ser + Gly213Gln + Thr214Gln

Pro195Asn + Gly196Pro + Asn198Ser + Gln200Glu + Thr202Ser + Thr207Gln + Tyr208Ala + Ala209Glu + Leu211Ala + Asn212Gln

Pro195Gly + Gly196Asn + Vall99Gln + Thr202Gly + Pro204Glu 35 + Glv205Gln + Ser206Glu + Thr207Ser + Leu211Gln + Asn212Gln

Pro195Gly + Gln200Asn + Tyr203Leu + Pro204Glu + Ser206Asp + Tyr208Gln + Ala209Gln + Asn212Gln + Gly213Pro +

40 Thr214Gln Ala194His + Pro195Ser + Val199Thr + Thr202Gly + Tyr203Cys + Pro204Glu + Ser206Glu + Leu2llHis + Asn212Ser +

Glv213Pro Prol95Gln + Val197Gln + Asn198Gln + Gln200Ser + Pro204Glu

+ Glv205Ser + Ser206Asp + Ala209Gly + Asn212Ser + 45 Thr214Gln

Ala194Thr + Asn198Asp + Val199Ala + Gln200Asn + Glv205Pro + Tyr208Ser + Ala209Gly + Leu211Val + Asn212Glu + Gly213Gln

Alal94Gly + Pro195Gln + Val199Cys + Tyr203Leu + Pro204Ser + Gly205Glu + Thr207Asp + Ale209Gln + Asn212Gln + Thr214Glv

Pro195Gln + Val197Gln + Gln200Ser + Thr202Gln + Pro204Glu + Gly205Ser + Thr207Asp + Leu211His + Asn212Ser +

Thr214Ser

30

- Alal94Asn + Pro1955er + Val197Ser + Asn198Gln + Thr202Asn + Pro204Asp + Thr207Glu + Leu21lHis + Asn212Ser + Glv213Ser
- 5 Ala194Thr + Pro195Ser + Val197Gin + Asn198Glu + Val199Met + Gln200Asp + Pro204Gly + Gly205Ser + Ala209Asn + Thv214Asn
 - Pro195Gln + Gly196Pro + Val197Met + Asn198Asp + Val199Ala + Gln200Glu + Thr202Pro + Tyr203Ile + Tyr20BCys + Leu21Iftr
- Gly213Asn Ala194Thr + Val197Pro + Val199His + Gln200Asp + Thr202Gln 15 + Tyr203Met + Gly205Ser + Thr207Asn + Tyr208Asp +
 - Asn212Ser Pro195Asn + Val197Asp + Asn198Gln + Val199Gly + Gin200Ser + Thr207Ser + Tyr208Ile + Ala209Asn + Asn212Ser +
- Gly213Asp 20 Pro195Asn + Val197Pro + Asn198Gln + Gln200Glu + Gly205Gln + Tyr208Gly + Ala209Gly + heu211Glu + Asn212Ser +
- Thr214Ser
 Ala194Thr + Gly196Ser + Asn198Ser + Gln260Asp + Thr202Gly
 + Tyr203Met + Gly205Gln + Tyr208Ala + Leu211Asp +
 - + Tyr203Met + Gly205Gin + Tyr208Ala + Leuz11A9p +
 Thr214Asn
 Pro195Ser + Asn198Ser + Val199Thr + Thr202Asn + Gly205Asn
 - + Thr2075er + Asn209Gly + Leu211Glu + Asn212Gln + Gly213Asp
 - Proi95Gln + Gly196Gln + Asn1985er + Thr202Pro + Pro204Asn + Thr207Asp + Tyr208Gly + Ala209Asp + Leu211Ile + Asn212Ser
 - Ala194Gly + Pro195Gly + Asn198Ser + Gln200Asn + Thr202Asn + Tyr203Ala + Tyr208Vai + Ser210Glu + Asn212Asp + Thr214Gly
- 35 Ala194Gln + Pro195Gln + Asn198Gln + Gln200Asn + Thr202Gly + Tyr203Leu + Gly205Gln + Ala209Gln + Ser210Glu + Asn212Glu
 - Pro195Gln + Val197Gly + Val199Gly + Thr202Asn + Gly205Pro + Thr207Asn + Ala209Asn + Ser210Glu + Leu211Met + Asn212Glu
- 40 Asn212Glu Ala194Thr + Pro195Gly + Gly196Pro + Asn198Ser + Thr207Pro + Tyr208Cys + Ala209Ser + Ser210Glu + Leu211Ser +
 - Asn212Asp Ala194His + Pro195Ser + Gly196Gln + Val197Ala + Val199Asn + Tyr203Gln + Thr207Asn + Tyr206His + Ser210Asp + Asn212Glu
 - Ala194Gln + Pro195Asn + Gly196Ser + Val197Met + Pro204Ser + Gly205Pro + Thr207Ser + Tyr208Ala + Ser210Glu + Asp212Glu
- 50 Ala194Ser + Vall99Thr + Thr202Ser + Tyr203Ala + Pro204Asn + Gly205Pro + Ser210Asp + Leu211Ala + Asn212Asp + Thr214Pro
 - Pro195Asn + Thr202Gln + Pro204Ser + Thr207Gly + Tyr208Glu + Ala209Asn + Ser210Glu + Leu211Asn + Asn212Gln +

40

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Gly213Asn

- Glv196Asn + Val197Thr + Val199Thr + Pro204Ser + Thr207Gln + Tyr208Asp + Ser210Asp + Leu211Thr + Asn212Gln + Thr214Asn
- Ala194Asn + Pro195Asn + Val199Cys + Gln200Asn + Pro204Gln + Thr207Ser + Tyr208Glu + Ser210Asp + Leu211Ash + Asn212Gln
 - Ala194Thr + Gly196Pro + Val199His + Gln200Ser + Gly205Asn + Ser206Glu + Tvr208Glu + Ala209Thr + Leu211Met +
- 10 Thr214Ser Ala194Ser + Pro195Gln + Asn198Gln + Val199His + Pro204Asn + Glv205Gln + Ser206Glu + Tyr208Asp + Ala209Thr +
 - Gly213Asn Glv196Gln + Val197Met + Val199Ser + Gln200Ser + Thr202Asn
- + Pro204Asn + Tyr208Thr + Ala209Gln + Asn212Glu + 15 Thr214Aso
 - Val197Ala + Asn198Ser + Gln200Ser + Thr202Glv + Pro204Gln + Thr207Gln + Tyr208Gln + Ala209His + Asn212Glu + Thr214Asp
- Ala194Pro + Gly196Ser + Val197Asp + Val199Asn + Thr202Asn 20 + Tvr203Val + Thr207Gln + Ala209Asn + Ser210Glu + Asn212Gln
- Pro195Ser + Val197Glu + Asn198Gln + Val199Gln + Tyr203Leu + Tyr208Val + Ala209Asn + Asn212Gln + Gly213Pro + 25 Thr214Glu
 - Pro195Gln + Gly196Pro + Val197Asn + Asn198Glu + Gln200Ser + Pro204Asn + Gly205Asn + Leu211Cys + Asn212Gln + G1v213Asp
 - Pro195Gln + Gly196Pro + Val197Thr + Asn198Asp + Thr202Pro + Tyr203Gln + Thr207Gly + Ala209Glu + Gly213Ser + Thr214Ser
 - Ala194Ser + Pro195Gln + Val197Pro + Asn198Asp + Val199Ala + Tyr203Thr + Pro204Gln + Ala209Asp + Leu211Val + Asn212Ser
- Pro195Gly + Val197Glu + Asn198Gln + Gln200Asp + Tyr203His 35 + Pro204Ser + Thr207Gly + Tyr208His + Gly213Pro + Thr214Gly
 - Pro195Glv + Glv196Pro + Vall99Thr + Gln200Glu + Tyr203Met + Pro204Gln + Glv205Pro + Tyr208Ser + Asn212Asp + Glv213Pro
 - Glv196Pro + Val197Ser + Val199Pro + Gln200Glu + Thr207Gly + Ala209Gly + Leu211Gln + Asn212Asp + Gly213Pro + Thr214Asn
 - Ala194His + Pro195Gln + Gly196Asn + Val197Ser + Glm200Glu + Tyr203Ala + Pro204Asn + Gly205Ser + Thr207Pro + Asn212Glu
 - Ala194Ser + Pro195Asn + Gly196Pro + Asn198Ser + Val199Thr + Tyr2081le + Leu211Glu + Asn212Gln + Gly213Ser + Thr214Glu
- Ala194Pro + Pro195Asn + Asn198Ser + Val199Met + Tyr203Met + Gly205Pro + Thr207Pro + Tyr208Ser + Leu211Glu + Thr214Glu
 - Ala194His + Pro195Glm + Sly196Glm + Val199Pro + Tyr203His + Thr207Asn + Ala209Asp + Leu211Ala + Asn212Glu +

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Thr214Asn

- Alal94His + Gly196Gln + Thr202Ser + Tyr203Gly + Pro204Gly + Gly205Ser + Ser206Asp + Thr207Gin + Ala209Asp + Thr214Pro
- Pro195Gln + Thr202Ser + Pro204Gln + Gly205Pro + Ser206Asp + Tvr208Met + Ala209Glu + Asn212Gln + Glv213Frc +
 - Gly196Gln + Val197Pro + Thr202Asn + Tyr203Gly + Gly205Pro + Ser206Glu + Thr207Ser + Ala209Glu + Leu211Gln + Asn212Ser
 - Ala194Asn + Pro195Ser + Gly196Pro + Val199Ala + Thr202Gln + Pro204Gln + Ser206Asp + Ala209Glu + Leu211His + Asn2125er
- Gly196Ser + Asn198Ser + Vall99Ser + Gln200Asn + Tyr203Asn + Gly205Gln + Ser206Glu + Ala209Glu + Leu211Ser + 15 Glv213Gln
 - Ala194Thr + Val197Cvs + Val199Asn + Pro204Glv + Ser206Asp + Thr207Glv + Tvr208Glv + Ala209Glu + Leu21111e + Thr214Gln
- Ala194Gly + Pro195Ser + Gln200Ser + Thr202Gly + Tyr203Leu + Pro204Glv + Gly205Pro + Ser206Asp + Ala209Asp + Thr214Glv
- Pro195Ser + Gly196Pro + Val199Nis + Gln200Asp + Thr202Pro + Gly205Pro + Thr207Asp + Ala209Thr + Asn212Gln + 25 G1v213G1n
 - Ala194Gln + Gly196Asn + Asn198Gln + Val199Pro + Gln200Asp + Thr202Gly + Tyr203Thr + Gly205Pro + Thr207Asp + Ala209Gln
- Pro195Asn + Val197Thr + Val199Ala + Gln200Asn + Tvr203Asn 30 + Gly205Pro + Thr207Gly + Ser210Asp + Asn212Gln + Glv213Glu
 - Ala194Asn + Pro195Gln + Val197Asn + Val199Asn + Pro204Gly + Thr207Pro + Ser210Asp + Asn212Ser + Gly213Glu +
- Ala194Gln + Pro195Asn + Val197Gly + Tyr203Met + Pro204Ser 35 + Tyr208Gln + Ala209Asn + Ser210Glu + Asn212Ser + G1v213G1u
- Alai94His + Gly196Ser + Tyr203Asn + Pro204Gly + Gly205Pro + Ala209Ser + Ser210Glu + Leu211Pro + Asn212Ser + 40
 - Glv213Asp Glv196Pro + Gln200Asn + Thr202Asn + Tyr203His + Gly205Asp + Tyr2081le + Ala209Glu + Leu211Met + Gly213Pro + Thr214Pro
 - Vall97Mis + Vall99Asn + Gln2G0Asn + Thr2G2Ser + Tyr2G3Ser + Gly205Glu + Tyr208Ser + Ala209Asp + Gly213Fro + Thr214Pro
 - Ala194Asn + Val197Pro + Gln206Ser + Thr202Gln + Tyr203Met + Gly205Gln + Thr207Asp + Ser210Asp + Leu211Ser + Ash212Ser
- Alal94Thr + Asn198Ser + Tyr203Asn + Gly205Pro + Thr207Asp + Ala209Gln + Ser210Glu + Leu211Val + Asn212Ser + Thr214Ser
 - Asn198Gln + Val199Pro + Gln20GAsn + Thr202Gln + Tyr203Asn + Thr207Asn + Ala209Pro + Ser210Glu + Asn212Ser +

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Glv213Asn

Ala194Ser + Pro195Asn + Asn198Gln + Val199Ala + Gln200Asp + Tyr203His + Ala209Thr + Leu211Ser + Gly213Asp + Thr214Ser

65

Alai94Pro + Pro195Asn + Gly196Pro + Val197Ser + Gln200Asp + Tvr208Cvs + Leu211Gln + Asn212Ser + Glv213Asp + Thr214Gly

Alai94Gln + Pro195Ser + Glv196Gln + Asnl98Asp + Gln200Ser + Thr202Ser + Tyr208Asp + Ala209Thr + Leu211His +

10 Thr214Asn Ala194Asn + Pro195Gln + Vall97Thr + Asn198Asp + Pro204Asn + Thr207Ser + Tyr208Asp + Leu211Ile + Gly213Gln +

Thr214Gln Ala194Gln + Pro195Asn + Val199Asn + Tyr203Ser + Pro204Asp

15 + Thr207Asn + Ser210Asp + Leu211Gly + Asn212Ser + Gly2135er

Ala194Asn + Pro195Asn + Thr202Glv + Pro204Asp + Tvr208Ile + Ala209Glv + Ser210Asp + Leu211Val + Asp212Glp + Thr214Ser

Ala194Asn + Gly196Ser + Asn198Ser + Val199Pro + Tyr203His + Pro204Glu + Glv205Gln + Tvr208Met + Ala209Thr + Ser210Glu

Alal94Thr + Asn198Ser + Val199Thr + Thr202Asn + Pro204Glu + Gly205Asn + Thr207Gln + Ala209His + Ser210Glu + Thr214Gly

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Ala194His + Pro195Gln + Asn198Ser + Val199Glv + Tvr203Gln + Pro204Asp + Thr207Gly + Ser210Glu + Asn212Gln + Glv213Ser

Pro195Asn + Tvr203Ser + Pro204Glu + Glv205Pro + Tvr208His + Ala209Glv + Ser210Glu + Leu211Pro + Glv213Pro + Thr214Asn

Gly196Asn + Asn198Ser + Gln200Ser + Thr202Gly + Pro204Asp + Gly205Asn + Ala209Thr + Ser210Glu + Gly213Pro + Thr214Ser

Gln200Ser + Thr202Gln + Tyr203Met + Pro204Asp + Gly205Pro 35 + Tyr208Cys + Ala209Glv + Ser210Asp + Leu211Thr +

Ala194Pro + Gly196Asn + Gln200Ser + Tyr203Ser + Pro204Glu + Thr207Gly + Ala209Asn + Ser210Asp + Leu211Val +

40 Thr214Ser Val199His + Gln200Ser + Thr202Ser + Pro204Asp + Gly205Asn

+ Tyr208Pro + Ser210Asp + Leu211Pro + Gly213Pro + Thr214Pro Ala194Ser + Pro195Asn + Gly196Ser + Val197Ser + Asn198Gln

+ Val199Ser + Pro204Glu + Tyr208Leu + Ser210Asp + 45

Ala194His + Gly196Pro + Val199Gly + Gln200Asp + Pro204Glu + Tyr208Gln + Ala209Gly + Leu2llSer + Asn212Ser + Thr214Asn

Alai94Gln + Vali97Pro + Vali99Asn + Gln200Asp + Thr202Gln + Pro204Asp + Gly205Asn + Tyr208His + Ala209Asn + Leu21111e

Pro195Ser + Val197Met + Asn198Ser + Gln200Asp + Thr202Gly + Tyr203Gln + Pro204Glu + Thr207Pro + Asn212Ser +

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Thr214Glv Pro195Ser + Val199Met + Gln200Ser + Pro204Gln + Thr207Ser + Ala209Glu + Leu211Ala + Asn212Gln + Gly213Glu + Thr214Gly

96

- Pro195Gln + Gly196Pro + Asn198Ser + Val199Gly + Tvr203Asn + Gly205Asn + Thr207Pro + Ala209Glu + Leu211Val + Gly213Asp
 - Ala194Asn + Pro195Gln + Asn198Ser + Val199Ser + Glv205Asn + Thr207Glu + Ala209Ser + Leu211Glu + Asn212Gln + Thr214Ser
 - Ala194Ser + Asn196Ser + Gin200Ser + Thr202Gly + Tvr203Leu + Thr207Gly + Ala209His + Ser210Glu + Asn212Ser + Thr214Asp
- Gly196Ser + Gln200Asn + Thr202Pro + Tyr203Leu + Pro204Asn 15 + Thr207Gln + Ser210Asp + Leu211Ala + Glv213Pro +
 - Gly196Ser + Asn198Gln + Tyr203Glv + Pro204Gln + Gly205Pro + Thr207Pro + Tyr208His + Ser210Glu + Gly213Gln + Thr214Asp
- Vall97Thr + Vall99Thr + Gln200Ser + Thr202Ser + Gly205Asn + Thr207Pro + Tvr208Cvs + Ser210Glu + Glv213Ser + Thr214Asp
- Gly196Gln + Val197Thr + Gln200Asp + Thr202Asn + Tyr203His + Ser206Glu + Thr207Ser + Tyr208Pro + Leu211Pro + Asn212Gln

- Vall97Met + Vall99Gln + Gln200Glu + Thr202Gln + Pro204Gln + Gly205Asn + Ser206Asp + Thr207Gln + Leu211Val + Thr214Ser
- Ala194Thr + Pro195Gly + Gly196Asn + Val197Ser + Gln200Glu + Thr202Pro + Gly205Pro + Ser206Glu + Leu211Met + Asn212Ser
 - Pro195Ser + Glv196Gln + Val199Cvs + Gln200Glu + Ser206Glu + Tyr208Thr + Leu211Gln + Asn212Gln + Glv213Pro + Thr214Asn
- Gly196Gln + Val197Gly + Asn198Gln + Gln200Glu + Glv205Asn + Ser206Glu + Thr207Pro + Ala209Asn + Asn212Gln + Gly213Ser
- Pro195Gln + Val197Glv + Gln200Glu + Tbr202Gln + Tvr203Val + Glv205Gln + Ser206Asp + Tyr208Met + Ala209Pro + 40 Thr21461v
 - Alai94Ser + Pro195Asn + Vall97Thr + Vall99Thr + Gln200Glu + Thr202Pro + Tyr203Ser + Gly205Pro + Ser206Glu + Thr214Gly
 - Pro195Ser + Gln200Glu + Thr202Gln + Tyr203Gly + Gly205Pro + Ser206Asp + Thr207Glv + Ala209His + Leu211His + Thr214Glv
 - Alai94Asn + Pro195Gly + Glv196Asn + Vall97Cys + Vall99Asn + Gln200Glu + Tyr203Pro + Pro204Gln + Ser206Asp + Leu211Ala
- Ala194Thr + Pro195Asn + Gly196Gln + Val197Asn + Gln200Glu + Thr202Ser + Ser206Glu + Ala209His + Leu211Ala + Thr214Ser
 - Val199Glv + Gln200Glu + Thr202Gln + Pro204Asn + Glv205Fro + Ser206Asp + Thr207Ser + Ala209Gly + Leu211Cvs +

Asn212Ser

- Ala194Thr + Val197Ser + Val199Gln + Gln200Asp + Thr202Gln + Pro204Gln + Ser205Glu + Ala209Gly + Leu211His + Glv213Gln
- 5 Alal94Gly + Gly196Asn + Asn198Gln + Gln200Glu + Gly205Pro + Ser206Asp + Ala209His + Leu211Pro + Gly213Gln + Thr214Gly
 - Gly196Ser + Val199Ser + Thr20ZSer + Pro204Asp + Thr207Asn + Tyr208Leu + Leu211Glu + Asn212Gln + Gly213Ser + Thr214Pro
 - Ala194Pro + Pro195Asn + Val197Pro + Thr202Pro + Tyr203Thr + Thr207Gln + Tyr208Glu + Asn212Glu + Gly21JSer + Thr214Ser
- Gly196Asn + Gln200Ser + Gly205Pro + Thr207Gln + Tyr208Asp + Ala229Ser + Leu211Ser + Asn212Glu + Gly213Pro +
 - Alal94Gly + Val199Pro + Gln200Asp + Thr202Pro + Tyr203Cys + Pro204Gly + Ala209Gln + LeuZllCys + Asn212Gln + Thr214Asu
- Ala194Pro + Val197Thr + Thr202Gln + Tyr203Met + Pro204Asn + Ser206Asp + Tyr208His + Ala209His + Ser210Asp + Thr214Asn
 - Gly196Asn + Val197Cys + Thr202Asn + Tyr203Met + Gly205Pro + Ser206Asp + Thr207Gly + Ala209Pro + Ser210Asp + Gly213Gln
- Ala194Thr + Val197Ser + Val199His + Thr202Gln + Tyr203Ser + Ser206Asp + Thr207Ser + Ser210Asp + Gly213Pro + Thr214Pro
 - Ala194Thr + Pro195Ser + Gly196Asn + Val197Pro + Asn198Gin + Thr202Gin + Ser206Giu + Ser210Giu + Asn212Ser + Thr214Gly
- 35 Pro195Asn + Gly196Ser + Val197Ser + Asn198Gln + Thr202Asn + Tyr203Met + Ser206Glu + Ser210Asp + Asn212Gln + Thr214Gln

TABLE 33

Multi-loop Double Mutation Variants 40 Leu 94Gly + Gln200Glu Gln 57Ser + Asn 60Ser Val 93Gln + Gly213Asp Tvr102Cvs + Thr207Gly Ser154Glu + Asn198Gln 45 Leul24Ile + Ash198Gln Ala209Gly + Ser210Glu Gln 57Asp + Leu 94Glv Leu 94Ala + Serl54Glu SO Ser101Asp + Leu211Thr Alal31Glu + Glv196Gln Ser128Glu + Pro204Asn

	Ser103Asp	+	Prol29Asn
	Gly157Asn		Thr207Ser
	Gly 98Glu		Gly158Gln
	Gin200Asp		Ala209Pro
5	Asn 60Glu	-6-	Asn198Gln
	Leu 94Ile		Ser 99Asp
	Leu124Ile	+	Ser210Asp
	Serl26Glu	+	
	Val 93Ala	4	Pro127Asp
10	Gly157Pro	+	Ser210Asp
***	Vall97Gly	+	
	Gln185Glu	*	Ala194Thr
	Ser 97Glu	4	Tyr203Asn
	Glv100Pro	÷	
15	Ser210Asp	+	
27	Tyrl61Asn	4	Thr207Asp
	Leu124Ser	4	
	Gly 615er	+	Thr207Pro
	Gly 98Glu	4	
20	Gln200Asn	ų.	
20			
	Asp 58Glu		Ile105Cys
	Gly 61Pro		
	Leul24Asp		
or	Gln 57Glu		
25	Gln185Ser		Asn212Asp
	Phe183His		Val197Glu
	Asn 60Glu	*	
	Gly 59Asn	+	
	Gly155Asp	+	
30	Gly 63Gln	+	
	Thr 64Pro	÷	
	Leu 94Gln	4	
	Thr207Gly	÷	
	Gln185Asp	÷	
35	Gly 63Asn	÷	Ala209Asn
	Tyr208Met	÷	
	Ser210Glu		Leu211Asn
	Tyr102Ala	÷	Pro129Asn
	Gly125Glu		
40	Ser103Asp		
	Ser128Glu		
	Gly155Gln	÷	
	Gln 57Asn		
	Serl03Asp	4	
45	Gly125Ser	÷	
	Ile105Pro	÷	
	Pro204Asp	*	
	Tyr161Asp	÷	Thr207Asn
	Asnl98Ser	+	Ser210Asp
50	Gly 958er	4	
	Gly 59Gln	4	Ala156Glu
	Gly 98Gln	4	Tyr102Cys
	Ala181His	*	Thr207Glu
	Ser154Glu	÷	Pro204Ser